WEST Search History

DATE: Friday, July 18, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT; PLUR=YES; OP=OR			
L2	n-formyl-methionyl-leucyl and fibrosis	2	L2
L1	6391856.pn.	1	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. Document ID: US 6462020 B1

L2: Entry 1 of 2 File: USPT Oct 8, 2002

US-PAT-NO: 6462020
DOCUMENT-IDENTIFIER: US 6462020 B1

TITLE: Small peptides and methods for treatment of asthma and inflammation

DATE-ISSUED: October 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Houck; John C.	late of Seattle	WA		
MacDonald; Mary	Lynden	WA		

US-CL-CURRENT: 514/18; 530/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6391856 B1

L2: Entry 2 of 2 File: USPT May 21, 2002

US-PAT-NO: 6391856
DOCUMENT-IDENTIFIER: US 6391856 B1

TITLE: Method for treatment of allergic reaction using formyl peptide

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Houck; John C.	late of Seattle	WA		
Clagett; James	Snohomish	WA		

US-CL-CURRENT: 514/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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Terms	Documents
n-formyl-methionyl-leucyl and fibrosis	2

Display Format: CIT Change Format

Previous Page Next Page

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NEWS 4	Feb 24	TEMA now available on STN
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NEWS 6	Feb 26	PCTFULL now contains images
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NEWS 14	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 15	Apr 28	RDISCLOSURE now available on STN
NEWS 16	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 17	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 18	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 19	May 19	Simultaneous left and right truncation added to WSCA
NEWS 20	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 21	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 22	Jun 06	PASCAL enhanced with additional data
NEWS 23	Jun 20	2003 edition of the FSTA Thesaurus is now available
NEWS 24	Jun 25	HSDB has been reloaded
NEWS 25	Jul 16	Data from 1960-1976 added to RDISCLOSURE

NEWS EXPRESS	April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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FILE 'CEN' ENTERED AT 16:31:14 ON 18 JUL 2003
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=> s fibrosis and therapy
L1      100020 FIBROSIS AND THERAPY

=> s l1 and peptide
L2        7830 L1 AND PEPTIDE

=> s f-met-leu-phe
L3        2329 F-MET-LEU-PHE

=> s l3 and l1
L4          34 L3 AND L1

=> s cirrhosis
L5      260709 CIRRHOSIS

=> s pulmonary fibrosis
L6       70721 PULMONARY FIBROSIS

=> s l6 and l5
L7        2310 L6 AND L5

=> s l4 and l7
L8           2 L4 AND L7

=> d l8 ti abs ibib tot

L8   ANSWER 1 OF 2  USPATFULL
```

TI Seven transmembrane receptor polynucleotides, polypeptides, and antibodies

AB The present invention relates to novel human 7TM polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human 7TM polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human 7TM polypeptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:38361 USPATFULL

TITLE: Seven transmembrane receptor polynucleotides, polypeptides, and antibodies

INVENTOR(S): Ni, Jian, Germantown, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Fan, Ping, Potomac, MD, UNITED STATES

PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (2)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003028008	A1	20030206
APPLICATION INFO.:	US 2002-116252	A1	20020405 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-711909, filed on 15 Nov 2000, PENDING Continuation-in-part of Ser. No. WO 2000-US13737, filed on 19 May 2000, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-135167P	19990520 (60)
	US 1999-143616P	19990713 (60)
	US 1999-152934P	19990909 (60)
	US 2000-189029P	20000314 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

NUMBER OF CLAIMS: 22

EXEMPLARY CLAIM: 1

LINE COUNT: 10846

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 2 USPATFULL

TI Nucleic acids, proteins, and antibodies

AB The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:165193 USPATFULL

TITLE: Nucleic acids, proteins, and antibodies

INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086822	A1	20020704	
APPLICATION INFO.:	US 2001-764886	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
	US 2000-225758P	20000814	(60)
	US 2000-220963P	20000726	(60)
	US 2000-217496P	20000711	(60)
	US 2000-225447P	20000814	(60)
	US 2000-218290P	20000714	(60)
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	US 2000-226868P	20000822	(60)
	US 2000-216647P	20000707	(60)
	US 2000-225267P	20000814	(60)
	US 2000-216880P	20000707	(60)
	US 2000-225270P	20000814	(60)
	US 2000-251869P	20001208	(60)
	US 2000-235834P	20000927	(60)
	US 2000-234274P	20000921	(60)
	US 2000-234223P	20000921	(60)
	US 2000-228924P	20000830	(60)
	US 2000-224518P	20000814	(60)
	US 2000-236369P	20000929	(60)
	US 2000-224519P	20000814	(60)
	US 2000-220964P	20000726	(60)
	US 2000-241809P	20001020	(60)
	US 2000-249299P	20001117	(60)
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	US 2000-236367P	20000929	(60)
	US 2000-237039P	20001002	(60)
	US 2000-237038P	20001002	(60)
	US 2000-236370P	20000929	(60)
	US 2000-236802P	20001002	(60)
	US 2000-237037P	20001002	(60)
	US 2000-237040P	20001002	(60)
	US 2000-240960P	20001020	(60)
	US 2000-239935P	20001013	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE,

```
                        ROCKVILLE, MD, 20850
NUMBER OF CLAIMS:       24
EXEMPLARY CLAIM:        1
LINE COUNT:             20931
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d his

     (FILE 'HOME' ENTERED AT 16:30:38 ON 18 JUL 2003)

     FILE 'MEDLINE, USPATFULL, DGENE, EMBASE, WPIDS, FSTA, HCAPLUS, BIOSIS,
     CEN' ENTERED AT 16:31:14 ON 18 JUL 2003
L1        100020 S FIBROSIS AND THERAPY
L2          7830 S L1 AND PEPTIDE
L3          2329 S F-MET-LEU-PHE
L4            34 S L3 AND L1
L5        260709 S CIRRHOSIS
L6         70721 S PULMONARY FIBROSIS
L7          2310 S L6 AND L5
L8             2 S L4 AND L7

=> d l4 ti abs ibib 1-10

L4   ANSWER 1 OF 34  USPATFULL
TI     Methods for producing high titre vectors and compositions used in such
       methods
AB     A method for producing viral vectors is described using packaging and
       producer cell lines is described. The producer cell comprises: (i) a
       first nucleotide sequence (NS) encoding a toxic viral envelope protein
       operably linked to a promoter; wherein the promoter is operably linked
       to at least one copy of a TRE; (ii) a second NS wherein the second NS
       comprises a sequence encoding a tetracycline modulator; (iii) a third NS
       encoding a retrovirus nucleocapsid protein; and (iv) a fourth NS
       comprising a retroviral sequence capable of being encapsidated in the
       nucleocapsid protein such that the retroviral vector particle titre
       obtainable from the producer cell is regulatable by tetracycline and an
       initial stimulus with sodium butyrate or functional analogues thereof.

ACCESSION NUMBER:       2003:166042  USPATFULL
TITLE:                  Methods for producing high titre vectors and
                        compositions used in such methods
INVENTOR(S):            Olsen, John C., Chapel Hill, NC, UNITED STATES
                        Mitrophanous, Kyriacos Andreou, Oxford, UNITED KINGDOM
                        Rohll, Jonathan, Oxford, UNITED KINGDOM
                        Kingsman, Alan John, Oxford, UNITED KINGDOM
                        Ellard, Fiona Margaret, Berkshire, UNITED KINGDOM
PATENT ASSIGNEE(S):     Oxford Biomedica (UK) Limited (U.S. corporation)

                             NUMBER        KIND    DATE
                        ---------------- ------ --------
PATENT INFORMATION:     US 2003113898      A1   20030619
APPLICATION INFO.:      US 2002-134643     A1   20020430  (10)

                               NUMBER        DATE
                        ------------------ --------
PRIORITY INFORMATION:   CA 2001-2344208    20010430
                        US 2001-287048P    20010430 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW,
                        WASHINGTON, DC, 20007
NUMBER OF CLAIMS:       40
EXEMPLARY CLAIM:        1
```

NUMBER OF DRAWINGS: 59 Drawing Page(s)
LINE COUNT: 4078

L4 ANSWER 2 OF 34 USPATFULL
TI Seven transmembrane receptor polynucleotides, polypeptides, and antibodies
AB The present invention relates to novel human 7TM polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human 7TM polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human 7TM polypeptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:38361 USPATFULL
TITLE: Seven transmembrane receptor polynucleotides, polypeptides, and antibodies
INVENTOR(S): Ni, Jian, Germantown, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Soppet, Daniel R., Centreville, VA, UNITED STATES
Li, Yi, Sunnyvale, CA, UNITED STATES
Fan, Ping, Potomac, MD, UNITED STATES
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (2)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003028008	A1	20030206
APPLICATION INFO.:	US 2002-116252	A1	20020405 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-711909, filed on 15 Nov 2000, PENDING Continuation-in-part of Ser. No. WO 2000-US13737, filed on 19 May 2000, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-135167P	19990520 (60)
	US 1999-143616P	19990713 (60)
	US 1999-152934P	19990909 (60)
	US 2000-189029P	20000314 (60)

Considered

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 10846
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 3 OF 34 USPATFULL
TI Small peptides and methods for treatment of asthma and inflammation
AB Methods for treating allergies, cutaneous inflammation, arthritis, chronic obstruction pulmonary disease and treating chronic inflammatory bowel disease are described. Also described is a method for inhibiting the infiltration of eosinophils into airways of a patient, a method for inhibiting the mucous release into airways of a patient, a method for blocking IgE activation of a lymphocyte, a method for stabilizing the cell membrane of a lymphocyte, thereby preventing their further involvement in the increased inflammatory response to an IgE antigen challenge, and a method for inhibiting the migration of T-cells. Such methods involve administering to said patient a therapeutically effective amount of a peptide having the formula f-Met-Leu-X, wherein X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe and Phe-Tyr.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2003:17906 USPATFULL
TITLE: Small peptides and methods for treatment of asthma and inflammation
INVENTOR(S): Houck, John C., Seattle, WA, UNITED STATES
Clagett, James, Snohomish, WA, UNITED STATES
PATENT ASSIGNEE(S): Hisatek, LLC (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003013658	A1	20030116
APPLICATION INFO.:	US 2002-147633	A1	20020516 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-190043, filed on 10 Nov 1998, GRANTED, Pat. No. US 6391856

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-65336P	19971113 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DIKE, BRONSTEIN, ROBERTS AND CUSHMAN,, INTELLECTUAL PROPERTY PRACTICE GROUP, EDWARDS & ANGELL, LLP., P.O. BOX 9169, BOSTON, MA, 02209
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 1511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 4 OF 34 USPATFULL
TI NUCLEIC ACIDS ENCODING PF4A RECEPTOR
AB cDNAs encoding a class of receptors, including the IL-8 receptors, have been identified in human tissue. Recombinantly produced PF4ARs are used in the preparation and purification of antibodies capable of binding to the receptors, and in diagnostic assays. The antibodies are advantageously used in the prevention and treatment of inflammatory conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:300813 USPATFULL
TITLE: NUCLEIC ACIDS ENCODING PF4A RECEPTOR
INVENTOR(S): LEE, JAMES, SAN BRUNO, CA, UNITED STATES
WOOD, WILLIAM I., SAN MATEO, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002168356	A1	20021114
APPLICATION INFO.:	US 1998-104063	A1	19980624 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-701265, filed on 22 Aug 1996, GRANTED, Pat. No. US 5776457
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GENENTECH INC, 1 DNA WAY, SOUTH SAN FRANCISCO, CA, 940804990
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 2796
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 5 OF 34 USPATFULL
TI Nucleic acids, proteins, and antibodies
AB The present invention relates to novel proteins. More specifically,

isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:165193 USPATFULL

TITLE: Nucleic acids, proteins, and antibodies

INVENTOR(S): Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Olney, MD, UNITED STATES
Barash, Steven C., Rockville, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002086822	A1	20020704	
APPLICATION INFO.:	US 2001-764886	A1	20010117	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-179065P	20000131	(60)
	US 2000-180628P	20000204	(60)
	US 2000-214886P	20000628	(60)
	US 2000-217487P	20000711	(60)
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	US 2000-229344P	20000901	(60)
	US 2000-234997P	20000925	(60)
	US 2000-229343P	20000901	(60)
	US 2000-229345P	20000901	(60)

	US 2000-229287P 20000901 (60)
	US 2000-229513P 20000905 (60)
	US 2000-231413P 20000908 (60)
	US 2000-229509P 20000905 (60)
	US 2000-236367P 20000929 (60)
	US 2000-237039P 20001002 (60)
	US 2000-237038P 20001002 (60)
	US 2000-236370P 20000929 (60)
	US 2000-236802P 20001002 (60)
	US 2000-237037P 20001002 (60)
	US 2000-237040P 20001002 (60)
	US 2000-240960P 20001020 (60)
	US 2000-239935P 20001013 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS:	24
EXEMPLARY CLAIM:	1
LINE COUNT:	20931

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 6 OF 34 USPATFULL

TI Method for treatment of allergic reaction using formyl peptide

AB Methods for treating allergies, cutaneous inflammation, arthritis, chronic obstruction pulmonary disease and treating chronic inflammatory bowel disease are described. Also described is a method for inhibiting the infiltration of eosinophils into airways of a patient, a method for inhibiting the mucous release into airways of a patient, a method for blocking IgE activation of a lymphocyte, a method for stabilizing the cell membrane of a lymphocyte; thereby preventing their further involvement in the increased inflammatory response to an IgE antigen challenge, and a method for inhibiting the migration of T-cells. Such methods involve administering to said patient a therapeutically effective amount of a peptide having the formula f-Met-Leu-X, wherein X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe and Phe-Tyr.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:116255 USPATFULL
TITLE:	Method for treatment of allergic reaction using formyl peptide
INVENTOR(S):	Houck, John C., late of Seattle, WA, United States deceased Mary MacDonald, United States executor Clagett, James, Snohomish, WA, United States
PATENT ASSIGNEE(S):	Histatek, LLC, San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6391856	B1	20020521
APPLICATION INFO.:	US 1998-190043		19981110 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-65336P	19971113 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Borin, Michael
LEGAL REPRESENTATIVE:	Neuner, George W., Edwards & Angell, LLP
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	26 Drawing Figure(s); 18 Drawing Page(s)

LINE COUNT: 1428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 7 OF 34 USPATFULL
TI Hydroxyl-containing bicyclic compounds
AB Disclosed are therapeutic compounds having the formula:

(R)j-(core moiety),

including resolved enantiomers, diastereomers, hydrates, salts, solvates and mixtures thereof. j is an integer from one to three, the core moiety is either non-cyclic or comprises at least one five- to seven-membered ring structure, R may be selected from the group consisting of hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted benzyl, C.sub.1-6 alkyl or C.sub.1-6 alkenyl, and at least one R has the formula I: ##STR1## n is an integer from seven to twenty and at least one of X or Y is --OH. The other of X or Y, which is not --OH, is hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --, and each W.sub.1, W.sub.2, and W.sub.3 is independently hydrogen, CH.sub.3 --, CH.sub.3 --CH.sub.2 --, CH.sub.3 --(CH.sub.2).sub.2 -- or (CH.sub.3).sub.2 --CH.sub.2 --. The X, Y, W.sub.1, W.sub.2, or W.sub.3 alkyl groups may be unsubstituted or substituted by an hydroxyl, halo or dimethylamino group. The disclosed compounds and therapeutic compositions thereof are useful in treating individuals having a disease or treatment-induced toxicity, mediated by second messenger activity.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2000:138360 USPATFULL
TITLE: Hydroxyl-containing bicyclic compounds
INVENTOR(S): Underiner, Gail E., Brier, WA, United States
Porubek, David, Seattle, WA, United States
Klein, J. Peter, Vashon Island, WA, United States
Woodson, Paul, Edmonds, WA, United States
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6133274		20001017
APPLICATION INFO.:	US 1996-756703		19961126 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-153256, filed on 16 Nov 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-976353, filed on 16 Nov 1992, now patented, Pat. No. US 5473070
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ford, John M.
ASSISTANT EXAMINER: Sripada, Pavanaram K
LEGAL REPRESENTATIVE: McDermott, Will & Emery
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1646
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 8 OF 34 USPATFULL
TI Therapeutic compounds containing xanthinyl
AB Therapeutic compounds with at least one carboxylic acid, ester or amide-substituted side chain have the formula:

CORE MOIETY --(R).sub.j

wherein j is an integer from one to three. The core moiety is non-cyclic

or cyclic (carbocyclic or heterocyclic). R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(2-10) alkenyl, carbocyclic or heterocyclic groups and at least one R has the formula I: ##STR1## wherein: one or two p are the integer one, otherwise p is two; and n is an integer from three to twenty; R.sub.1 is selected from the group consisting of substituted and unsubstituted CH.sub.2 ; NR.sub.3, R.sub.3 being hydrogen, substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or C.sub.(1-20) hydroxyalkyl, or carbocyclic or heterocyclic group; O; --CHR.sub.4 O--, R.sub.4 being substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl, C.sub.(1-20) hydroxyalkyl, or R.sub.2 and R.sub.4 join to form a substituted or unsubstituted heterocycle having four to seven ring atoms, the ether group --O-- of --CHR.sub.4 O-- being a member of the heterocycle. R.sub.2 is selected from the group consisting of hydrogen; halogen; substituted or unsubstituted C.sub.(1-10) alkyl; C.sub.(1-10) alkoxyl; C.sub.(2-10) alkenyl; C.sub.(1-10) hydroxyallyl; --A(R.sub.5).sub.m, A being N or O, m being one or two and R.sub.5 being hydrogen, a substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxyl, C.sub.(2-10) alkenyl or C.sub.(1-10) hydroxyalkyl), or carbocyclic or heterocyclic group. At least one of R.sub.1 is NR.sub.3, O or --CHR.sub.4 O--, or R.sub.2 is --A(R.sub.5).sub.m. The compounds and pharmaceutical compositions thereof are useful as therapies for diseases advanced via intracellular signaling through specific intracellular signaling pathways by mediating a signaling response to an external stimuli.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2000:102304 USPATFULL		
TITLE:	Therapeutic compounds containing xanthinyl		
INVENTOR(S):	Klein, J. Peter, Vashon, WA, United States Leigh, Alistair J., Brier, WA, United States Underiner, Gail E., Brier, WA, United States Kumar, Anil M., Seattle, WA, United States		
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6100271		20000808
APPLICATION INFO.:	US 1995-483871		19950607 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1994-199368, filed on 18 Feb 1994, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Berch, Mark L.		
LEGAL REPRESENTATIVE:	McDermott, Will & Emery		
NUMBER OF CLAIMS:	14		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)		
LINE COUNT:	1986		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 9 OF 34 USPATFULL

TI PF4A receptor

AB cDNAs encoding a class of receptors, including the IL-8 receptors, have been identified in human tissue. Recombinantly produced PF4ARs are used in the preparation and purification of antibodies capable of binding to the receptors, and in diagnostic assays. The antibodies are advantageously used in the prevention and treatment of inflammatory conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2000:88302 USPATFULL

TITLE: PF4A receptor
INVENTOR(S): Lee, James, San Bruno, CA, United States
Wood, William I., San Mateo, CA, United States
PATENT ASSIGNEE(S): Genentech, Inc., So. San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6087475		20000711
APPLICATION INFO.:	US 1998-104296		19980624 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-701265, filed on 22 Aug 1996, now patented, Pat. No. US 5776457 which is a continuation of Ser. No. US 1996-664228, filed on 6 Jun 1996, now abandoned which is a continuation of Ser. No. US 1993-76093, filed on 11 Jun 1993, now patented, Pat. No. US 5543503 which is a continuation-in-part of Ser. No. US 1991-810782, filed on 19 Dec 1991, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ulm, John
LEGAL REPRESENTATIVE: Love, Richard B.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 23 Drawing Figure(s); 17 Drawing Page(s)
LINE COUNT: 2844
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 10 OF 34 USPATFULL
TI Methods for using therapeutic compounds containing xanthinyl
AB Therapeutic compounds with at least one carboxylic acid, ester or amide-substituted side chain have the formula:

CORE MOIETY --(R).sub.j

wherein j is an integer from one to three. The core moiety is non-cyclic or cyclic (carbocyclic or heterocyclic). R may be selected from among hydrogen, halogen, hydroxyl, amino, substituted or unsubstituted C(.sub.1-10) alkyl, C(.sub.2-10) alkenyl, carbocyclic or heterocyclic groups and at least one R has the formula I: ##STR1## wherein: one or two p are the integer one, otherwise p is two; and n is an integer from three to twenty; R.sub.1 is selected from the group consisting of substituted and unsubstituted CH.sub.2 ; NR.sub.3, R.sub.3 being hydrogen, substituted or unsubstituted C(.sub.1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl or C.sub.(1-20) hydroxyalkyl, or carbocyclic or heterocyclic group; O; --CHR.sub.4 O--, R.sub.4 being substituted or unsubstituted C.sub.(1-20) alkyl, C.sub.(1-20) alkoxyl, C.sub.(2-20) alkenyl, C.sub.(1-20) hydroxyalkyl, or R.sub.2 and R.sub.4 join to form a substituted or unsubstituted heterocycle having four to seven ring atoms, the ether group --O-- of --CHR.sub.4 O-- being a member of the heterocycle. R.sub.2 is selected from the group consisting of hydrogen; halogen; substituted or unsubstituted C.sub.(1-10) alkyl; C.sub.(1-10) alkoxyl; C.sub.(2-10) alkenyl; C.sub.(1-10) hydroxyalkyl; --A(R.sub.5).sub.m, A being N or 0, m being one or two and R.sub.5 being hydrogen, a substituted or unsubstituted C.sub.(1-10) alkyl, C.sub.(1-10) alkoxyl, C.sub.(2-10) alkenyl or C.sub.(1-10) hydroxyalkyl), or carbocyclic or heterocyclic group. At least one of R.sub.1 is NR.sub.3, O or --CHR.sub.4 O--, or R.sub.2 is --A(R.sub.5).sub.m. The compounds and pharmaceutical compositions thereof are useful as therapies for diseases advanced via intracellular signaling through specific intracellular signaling pathways by mediating a signaling response to an external stimuli.

ACCESSION NUMBER: 2000:37806 USPATFULL
TITLE: Methods for using therapeutic compounds containing

	xanthinyl
INVENTOR(S):	Klein, J. Peter, Vashon, WA, United States Leigh, Alistair J., Brier, WA, United States Underiner, Gail E., Brier, WA, United States Kumar, Anil M., Seattle, WA, United States Rice, Glenn C., Seattle, WA, United States
PATENT ASSIGNEE(S):	Cell Therapeutics, Inc., Seattle, WA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6043250		20000328
APPLICATION INFO.:	US 1995-472296		19950607 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1994-199368, filed on 18 Feb 1994, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Travers, Russell		
LEGAL REPRESENTATIVE:	McDermott, Will & Emery		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Page(s)		
LINE COUNT:	2052		

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=> s antifibrotic?
L9        2635 ANTIFIBROTIC?

=> s fibrolysis
L10        193 FIBROLYSIS

=> s l9 and l10
L11         25 L9 AND L10

=> d l11 ti abs ibib tot

L11  ANSWER 1 OF 25     MEDLINE
TI   Hepatitis C and liver fibrosis.
AB   Chronic hepatitis C progresses to cirrhosis within 20 years in an
     estimated 20-30% of patients, while running a relatively uneventful course
     in most others.  Certain HCV proteins, such as core and NS5A, can induce
     derangement of lipid metabolism or alter signal transduction of infected
     hepatocytes which leads to the production of reactive oxygen radicals and
     profibrogenic mediators, in particular TGF-beta1.  TGF-beta1 is the
     strongest known inducer of fibrogenesis in the effector cells of hepatic
     fibrosis, i.e. activated hepatic stellate cells and myofibroblasts.
     However, fibrogenesis proceeds only when additional profibrogenic stimuli
     are present, e.g. alcohol exposure, metabolic disorders such as
     non-alcoholic steatohepatitis, or coinfections with HIV or Schistosoma
     mansoni that skew the immune response towards a Th2 T cell reaction.
     Furthermore, profibrogenic polymorphisms in genes that are relevant during
     fibrogenesis have been disclosed.  This knowledge will make it possible to
     identify those patients who are most likely to progress and who need
     antiviral or antifibrotic therapies most urgently.  However,
     even the best available treatment, the combination of pegylated interferon
     and ribavirin, which is costly and fraught with side effects, eradicates
     HCV in only 50% of patients.  While the suggestive antifibrotic
     effect of interferons (IF-gamma>alpha,beta), irrespective of viral
     elimination, has to be proven in randomised prospective studies,
     additional, well tolerated and cost-effective antifibrotic
     therapies have to be developed.  The combination of cytokine strategies,
     e.g. inhibition of the key profibrogenic mediator TGF-beta, with other
     potential antifibrotic agents appears promising.  Such
     adjunctive agents could be silymarin, sho-saiko-to, halofuginone,
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phosphodiesterase inhibitors, and endothelin-A-receptor or angiotensin antagonists. Furthermore, drug targeting to the fibrogenic effector cells appears feasible. Together with the evolving validation of serological markers of hepatic fibrogenesis and **fibrolysis** an effective and individualised treatment of liver fibrosis is anticipated.Cell Death and Differentiation (2003) 10, S59-S67. doi:10.1038/sj.cdd.4401163

ACCESSION NUMBER: 2003139293 IN-PROCESS
DOCUMENT NUMBER: 22541015 PubMed ID: 12655347
TITLE: Hepatitis C and liver fibrosis.
AUTHOR: Schuppan D; Krebs A; Bauer M; Hahn E G
CORPORATE SOURCE: Department of Medicine I, University of Erlangen-Nuernberg, Germany.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2003 Jan) 10 Suppl 1 S59-67.
Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030326
Last Updated on STN: 20030326

Bad date

L11 ANSWER 2 OF 25 MEDLINE

TI Fibrosis of liver, pancreas and intestine: common mechanisms and clear targets?.

AB Chronic diseases of the liver, pancreas, intestine, kidneys, skin and lungs are usually accompanied by scarring. Loss of organ function is often progressive despite the use of immunosuppressive, antiviral or antiinflammatory agents. Therefore, well tolerated **antifibrotic** therapies are urgently needed. The targets for such therapies are activated mesenchymal cells that synthesize an excess of matrix proteins and resemble the myofibroblasts of healing wounds. These cells derive from normally quiescent fibroblasts or smooth muscle cells and from stellate cells of liver and pancreas. Their activation is triggered and maintained by mechanical stress and several fibrogenic modulators and cytokines. Some agents inhibit myofibroblast proliferation and collagen synthesis in vitro, but only few of them are effective in vivo. Potential **antifibrotic** drugs have been tested mainly in models of liver fibrosis. In the suitable rat model of biliary fibrosis, an **antifibrotic** effect was demonstrated for silymarin, a defined mixture of flavonoids, and to a lesser degree for pentoxifylline. A spin-off of the large multicenter trials for hepatitis C is the finding that interferon-alpha given for 6-12 months may halt or reverse fibrosis, even in virological non-responders. This has to be proven in prospective randomized trials. Specific inhibitors of the endothelin-A-receptor which are orally available can suppress liver collagen accumulation by 40-60%. Other strategies aim at inhibition of the profibrogenic cytokines TGF-beta or connective tissue growth factor. Effective drug targeting to the fibrogenic liver cells is now possible by use of cyclic peptides that bind to receptors which are specifically upregulated on activated stellate cells. Blockade of such activation receptors can induce stress-relaxation which reverts the fibrogenic cells to a fibrolytic, collagen degrading phenotype. Fibrosis has been discovered as a novel target for the pharmaceutical industry. This implies the use of combinatorial chemistry and an automatized screening machinery, greatly speeding up the design and selection of specific **antifibrotic** agents. Combined with the rapidly evolving validation of serological markers of fibrogenesis and **fibrolysis** unforeseen progress in the treatment of organ fibrosis can be expected.

ACCESSION NUMBER: 2001195680 MEDLINE
DOCUMENT NUMBER: 21129179 PubMed ID: 11233519
TITLE: Fibrosis of liver, pancreas and intestine: common mechanisms and clear targets?.
AUTHOR: Schuppan D; Koda M; Bauer M; Hahn E G

CORPORATE SOURCE: Medizinische Klinik I, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Germany.
SOURCE: ACTA GASTROENTEROLOGICA BELGICA, (2000 Oct-Dec) 63 (4) 366-70. Ref: 29
Journal code: 0414075. ISSN: 0001-5644.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

L11 ANSWER 3 OF 25 MEDLINE

TI Intralesional recombinant interferon alpha-2b in Peyronie's disease.

AB OBJECTIVE: To evaluate interferon alpha-2b (IFN) in the treatment of Peyronie's disease (PD) since IFN exerts **antifibrotic** action through collagen synthesis inhibition and **fibrolysis** stimulation. METHODS: The study comprised 34 patients, aged 31 to 63, with clinical and ultrasonographic (US) diagnosis of PD, who gave their consent to enter the study. They had the disease for 10.1 +/- 5.6 (2-22) months. Ten million IU of IFN were injected intralesionally, twice weekly for 14 weeks or less if there was complete remission. Clinical evaluation included penis angle at erection, sexual dysfunction (pain, possibility of intercourse) and palpable plaque. Plaque size was evaluated by US. Systemic and local adverse reactions, and anti-IFN antibodies were monitored as well. RESULTS: Sexual dysfunction disappeared in 19/24 (79.2%) patients with this disorder, palpable lesions in 21/34 (62%), angle at erection in 15/32 (47%), and pain in 16/17 (94%). Complete clinical response was achieved in 16/34 patients (47%). Ultrasonographic response rate was 88%, (53% complete). Plaque size decreased from 56.7 +/- 42.9 (median: 35.4) before treatment to 12.7 +/- 22.6 mm2 (median: 0) ($p < 0.00001$; Wilcoxon's paired test). Clinical and US responses correlated. No patient showed progression. Eight of 9 patients in whom other treatments had failed responded to IFN therapy (5 complete). The main systemic adverse reaction in most patients (mild or moderate) was the flu-like syndrome expected for IFN. Local reactions, more related to the administration procedure than to IFN itself, were small hematoma (10 patients), edema (3), cysts that were excised surgically (2), and venous leak (1). No patient developed anti-IFN antibodies. CONCLUSIONS: IFN treatment can be a suitable option for the management of PD. The results appear to be better than those achieved with other procedures. Further work should include comparative studies, long-term follow-up of treated patients, and alternative ways of administration.

ACCESSION NUMBER: 2000488272 MEDLINE
DOCUMENT NUMBER: 20492265 PubMed ID: 11037665
TITLE: Intralesional recombinant interferon alpha-2b in Peyronie's disease.
AUTHOR: Astorga R; Cantero O; Contreras D; del Rio-Martin A; Labarta-Beceiro V; Gutierrez-Elvirez A; Lima-Lopez M A; Lopez-Saura P
CORPORATE SOURCE: General Calixto Garcia Hospital, Havana, Cuba.
SOURCE: ARCHIVOS ESPANOLES DE UROLOGIA, (2000 Sep) 53 (7) 665-71.
Journal code: 0064757. ISSN: 0004-0614.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322

Entered Medline: 20001102

L11 ANSWER 4 OF 25 MEDLINE
TI Interferon-alpha 2b increases **fibrolysis** in fibrotic livers from bile duct ligated rats: possible participation of the plasminogen activator.
AB Interferons are known to prevent liver collagen by an antifibrogenic mechanism that involves mRNA procollagen regulation. The aim of the present work was to determine whether interferon could also decrease collagen by increasing its degradation. Fibrosis was induced in male Wistar rats by double ligation and section of the common bile duct. Interferon-alpha 2b (100,000 IU/rat s.c.) was administered to bile duct ligated rats daily after surgery for 4 weeks. Interferon increased the capacity of the liver to degrade type I and III collagens and matrigel. In addition, the plasminogen activator activity also increased. Since plasminogens are thought to be key participants in the balance of proteolytic activities that regulate extracellular matrix degradation, their elevation may also provide another **antifibrotic** (proteolytic) mechanism of action of interferon.
ACCESSION NUMBER: 96401795 MEDLINE
DOCUMENT NUMBER: 96401795 PubMed ID: 8966190
TITLE: Interferon-alpha 2b increases **fibrolysis** in fibrotic livers from bile duct ligated rats: possible participation of the plasminogen activator.
AUTHOR: Rodriguez-Fragoso L; Gonzalez M P; Muriel P
CORPORATE SOURCE: Departamento de Gastroenterologia, Instituto Nacional de la Nutricion Salvador Zubiran, Mexico.
SOURCE: PHARMACOLOGY, (1995 Dec) 51 (6) 341-6.
Journal code: 0152016. ISSN: 0031-7012.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961205

L11 ANSWER 5 OF 25 MEDLINE
TI [Connective tissue polypeptides in serum: new parameters of connective tissue synthesis and degradation in liver fibrosis]. Bindegewebspolypeptide im Serum: neue Parameter von Bindegewebs-Synthese und -Abbau bei der Leberfibrose.
AB With the invention of drugs that effectively and specifically inhibit excessive collagen synthesis in the liver, a growing interest in serum assays that assess fibrogenesis, i.e. the de-novo formation and **fibrolysis**, i.e. the removal of connective tissue in the liver, may be anticipated. Several serum assays for connective tissue polypeptides fulfil the criteria of sensitivity and specificity for chronic liver diseases. The aminoterminal procollagen type III peptide (PIIINP) correlates with hepatic fibrogenesis, whereas the propeptides of basement membrane collagen (PIVNP and PIVCP) and the basement membrane glycoprotein laminin reflect the enhanced turnover of basement membranes of the sinusoids as well as of proliferating bile ducts and blood vessels in active fibrosis. Circulating collagen type VI results from degradation of interstitial microfilaments and undulin appears to be released upon remodeling of the hepatic architecture. Combined measurement of selected parameters may allow a non-invasive assessment of the balance between fibrogenesis and **fibrolysis** on a day-to-day basis, especially in the light of potential **antifibrotic** therapy.
ACCESSION NUMBER: 93079997 MEDLINE
DOCUMENT NUMBER: 93079997 PubMed ID: 1449013
TITLE: [Connective tissue polypeptides in serum: new parameters of connective tissue synthesis and degradation in liver

fibrosis].
Bindegewebspolypeptide im Serum: neue Parameter von Bindegewebs-Synthese und -Abbau bei der Leberfibrose.

AUTHOR: Schuppan D

CORPORATE SOURCE: Abteilung fur Gastroenterologie Universitatsklinikum Steglitz, Freien Universitat Berlin, Bundesrepublik Deutschland.

SOURCE: ZEITSCHRIFT FUR GASTROENTEROLOGIE, (1992 Mar) 30 Suppl 1 29-34. Ref: 34
Journal code: 0033370. ISSN: 0044-2771.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: German

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199212

ENTRY DATE: Entered STN: 19930129
Last Updated on STN: 19930129
Entered Medline: 19921229

L11 ANSWER 6 OF 25 MEDLINE

TI Connective tissue polypeptides in serum as parameters to monitor **antifibrotic** treatment in hepatic fibrogenesis.

AB With the potential to specifically inhibit hepatic collagen synthesis a demand for serum tests to monitor the effectiveness of such treatment is expected. Serum assays for connective tissue polypeptides offer the potential to assess the dynamics of accumulation, i.e., fibrogenesis, and removal, i.e., **fibrolysis**, of the hepatic connective tissue on a regular and frequent basis. Several assays for circulating connective tissue polypeptides may be of use in fibrogenic liver diseases. Whereas an increase of the aminoterminal propeptide of type III procollagen (PIIINP) appears to be related to fibrogenesis, the propeptides of type IV procollagen (PIVNP, PIVCP) and laminin mirror enhanced basement membrane turnover in active fibrosis. Collagen type VI (CVI) and undulin (Un) rather reflect **fibrolysis** and remodelling of the interstitial connective tissue. Although the circulating antigens measured by these assays are heterogeneous, which often complicates the interpretation of elevated serum levels, it is likely that firm conclusions can be drawn as to the ongoing fibrogenesis, **fibrolysis** or both, once individual patients are followed with a combined measurement of two or three of these connective tissue parameters. Since 'easy to perform' assays are currently developed, such as therapy control seems practicable.

ACCESSION NUMBER: 92268442 MEDLINE

DOCUMENT NUMBER: 92268442 PubMed ID: 1815006

TITLE: Connective tissue polypeptides in serum as parameters to monitor **antifibrotic** treatment in hepatic fibrogenesis.

AUTHOR: Schuppan D

CORPORATE SOURCE: Abteilung fur Gastroenterologie, Freien Universitat, Berlin, Federal Republic of Germany.

SOURCE: JOURNAL OF HEPATOLOGY, (1991) 13 Suppl 3 S17-25. Ref: 71
Journal code: 8503886. ISSN: 0168-8278.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199206

ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 19920710
Entered Medline: 19920623

L11 ANSWER 7 OF 25 USPATFULL
TI Treatment with small peptides to effect **antifibrotic** activity
AB Methods for treating treating fibrosis in a mammal are described. An **antifibrotic** effective amount of a peptide having the formula f-Met-Leu-X where X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe and Phe-Tyr is administered to the mammal. The fibrosis may be due to pathological changes resulting, e.g., from pulmonary fibrosis, atherosclerosis, cirrhosis, glomerulosclerosis, chronic pancreatitus, coronary artery disease (such as caused by infection by bacterium Chlamydia pneumoniae), trauma or surgical procedures. Examples of surgical procedures that cause fibrosis are post-operative fibrosis peri-neurally in the dura or nerve roots following spinal surgery, tenolysis of injured or repaired tendons with adhesions, neurolysis of damaged or repaired peripheral nerves with adhesions, post-operative adhesions from gynecologic and abdominal surgeries, reparative surgery of the vas deferens or fallopian tubes for reversal of male or female sterilization, and surgical repair of other tubular structures such as urethra, intestine or esophagus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:141513 USPATFULL		
TITLE:	Treatment with small peptides to effect **antifibrotic** activity		
INVENTOR(S):	Clagett, James, Snohomish, WA, UNITED STATES		
PATENT ASSIGNEE(S):	Histatek, Inc. (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002072499	A1	20020613
APPLICATION INFO.:	US 2001-960720	A1	20010921 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2000-US7411, filed on 20 Mar 2000, UNKNOWN		
	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-125514P	19990322 (60)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Edwards & Angell, LLP, P.O. Box 9169, Boston, MA, 02209		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	13 Drawing Page(s)		
LINE COUNT:	814		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 8 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Hepatitis C and liver fibrosis.
AB Chronic hepatitis C progresses to cirrhosis within 20 years in an estimated 20-30% of patients, while running a relatively uneventful course in most others. Certain HCV proteins, such as core and NS5A, can induce derangement of lipid metabolism or alter signal transduction of infected hepatocytes which leads to the production of reactive oxygen radicals and profibrogenic mediators, in particular TGF-.beta.1. TGF-.beta.1 is the strongest known inducer of fibrogenesis in the effector cells of hepatic fibrosis, i.e. activated hepatic stellate cells and myofibroblasts. However, fibrogenesis proceeds only when additional profibrogenic stimuli are present, e.g. alcohol exposure, metabolic disorders such as non-alcoholic steatohepatitis, or coinfections with HIV or Schistosoma mansoni that skew the immune response towards a Th2 T cell reaction. Furthermore, profibrogenic polymorphisms in genes that are relevant during fibrogenesis have been disclosed. This knowledge will make it possible to identify those patients who are most likely to progress and who need antiviral or **antifibrotic** therapies most urgently. However, even the best available treatment, the combination of pegylated interferon and

ribavirin, which is costly and fraught with side effects, eradicates HCV in only 50% of patients. While the suggestive **antifibrotic** effect of interferons (IF-.gamma.>.alpha.,.beta.), irrespective of viral elimination, has to be proven in randomised prospective studies, additional, well tolerated and cost-effective **antifibrotic** therapies have to be developed. The combination of cytokine strategies, e.g. inhibition of the key profibrogenic mediator TGF-.beta., with other potential **antifibrotic** agents appears promising. Such adjunctive agents could be silymarin, sho-saiko-to, halofuginone, phosphodiesterase inhibitors, and endothelin-A-receptor or angiotensin antagonists. Furthermore, drug targeting to the fibrogenic effector cells appears feasible. Together with the evolving validation of serological markers of hepatic fibrogenesis and **fibrolysis** an effective and individualised treatment of liver fibrosis is anticipated.

ACCESSION NUMBER: 2003172043 EMBASE
TITLE: Hepatitis C and liver fibrosis.
AUTHOR: Schuppan D.; Krebs A.; Bauer M.; Hahn E.G.
CORPORATE SOURCE: D. Schuppan, Department of Medicine I, University of Erlangen-Nuernberg, Ulmenweg 18, 91054 Erlangen, Germany. detlef.schuppan@med1.imed.uni-erlangen.de
SOURCE: Cell Death and Differentiation, (1 Jan 2003) 10/SUPPL. 1 (S59-S67).
Refs: 77
ISSN: 1350-9047 CODEN: CDDIEK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 9 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Hepatic fibrosis: From bench to bedside.
AB **Antifibrotic** therapies are preferentially targeted to the activated mesenchymal cells in the liver that synthesize an excess of matrix proteins and resemble the myofibroblasts of healing wounds. These cells derive from normally quiescent hepatic stellate cells and (myo-) fibroblasts. Their activation is triggered and maintained by several fibrogenic modulators and cytokines, but also by mechanical stress. Whereas many agents inhibit stellate cell/myofibroblast proliferation and collagen synthesis in vitro, only few of them are tolerable or effective in suitable animal models in vivo. An **antifibrotic** effect was demonstrated for silymarin, a defined mixture of flavonoids, sho-saiko-to which contains the related compound baicalein, for halofuginone, another plant-derived agent, for the phosphodiesterase inhibitor pentoxifylline and for LU135252, an oral inhibitor of the endothelin-A-receptor. The retrospective find-ing that interferon-.alpha. therapy for hepatitis C may halt or even reverse fibrosis, has to be confirmed in prospective randomized trials. Strategies to inhibit the profibrogenic cytokines transforming growth factor (TGF)-.beta. or connective tissue growth factor (e.g. by soluble decoy receptors) are evolving, but have not been convincing yet. Drug targeting to the fibrogenic liver cells is now possible by use of cyclic peptides that bind to receptors which are specifically up-regulated on activated stellate cells, for example those for platelet-derived growth factors or collagen type VI. In addition, blockade of such activation receptors can induce stress-relaxation which reverts the fibrogenic cells to a fibrolytic, collagen degrading phenotype. Combined with the evolving validation of serological markers of fibrogenesis and **fibrolysis** an effective and individualized treatment of liver fibrosis can be anticipated. .COPYRGT. 2002 Blackwell

Publishing Asia Pty Ltd.
ACCESSION NUMBER: 2002453840 EMBASE
TITLE: Hepatic fibrosis: From bench to bedside.
AUTHOR: Schuppan D.; Porov Y.
CORPORATE SOURCE: Dr. D. Schuppan, Department of Medicine I, Division of Gastroenterology, University of Erlangen-Nuernberg, Krankenhausstr. 12, 91054 Erlangen, Germany. detlef.schuppan@med1.med.uni-erlangen.de
SOURCE: Journal of Gastroenterology and Hepatology, (2002) 17/SUPPL. 3 (S300-S305).
Refs: 28
ISSN: 0815-9319 CODEN: JGHEEO
COUNTRY: Australia
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 10 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Fibrosis of liver, pancreas, and intestine: Common mechanisms and clear targets?.
AB Chronic diseases of the liver, pancreas, intestine, kidneys, skin and lungs are usually accompanied by scarring. Loss of organ function is often progressive despite the use of immunosuppressive, antiviral or antiinflammatory agents. Therefore, well tolerated **antifibrotic** therapies are urgently needed. The targets for such therapies are activated mesenchymal cells that synthesize an excess of matrix proteins and resemble the myofibroblasts of healing wounds. These cells derive from normally quiescent fibroblasts or smooth muscle cells and from stellate cells of liver and pancreas. Their activation is triggered and maintained by mechanical stress and several fibrogenic modulators and cytokines. Some agents inhibit myofibroblast proliferation and collagen synthesis in vitro, but only few of them are effective in vivo. Potential **antifibrotic** drugs have been tested mainly in models of liver fibrosis. In the suitable rat model of biliary fibrosis, an **antifibrotic** effect was demonstrated for silymarin, a defined mixture of flavonoids, and to a lesser degree for pentoxifylline. A spin-off of the large multicenter trials for hepatitis C is the finding that interferon-.alpha. given for 6-12 months may halt or reverse fibrosis, even in virological non-responders. This has to be proven in prospective randomized trials. Specific inhibitors of the endothelin-A-receptor which are orally available can suppress liver collagen accumulation by 40-60%. Other strategies aim at inhibition of the profibrogenic cytokines TGF-.beta. or connective tissue growth factor. Effective drug targeting to the fibrogenic liver cells is now possible by use of cyclic peptides that bind to receptors which are specifically up-regulated on activated stellate cells. Blockade of such activation receptors can induce stress-relaxation which reverts the fibrogenic cells to a fibrolytic, collagen degrading phenotype. Fibrosis has been discovered as a novel target for the pharmaceutical industry. This implies the use of combinatorial chemistry and an automatized screening machinery, greatly speeding up the design and selection of specific **antifibrotic** agents. Combined with the rapidly evolving validation of serological markers of fibrogenesis and **fibrolysis** unforeseen progress in the treatment of organ fibrosis can be expected.
ACCESSION NUMBER: 2001066184 EMBASE
TITLE: Fibrosis of liver, pancreas, and intestine: Common mechanisms and clear targets?.
AUTHOR: Schuppan D.; Koda M.; Bauer M.; Hahn E.G.
CORPORATE SOURCE: Dr. D. Schuppan, Dept. of Medicine I, Div. Gastroenter., Hepatol./Intect., University of Erlangen-Nuernberg,

Krankenhausstr. 12, 91054 Erlangen, Germany
SOURCE: Acta Gastro-Enterologica Belgica, (2000) 63/4 (366-370).
Refs: 29
ISSN: 0001-5644 CODEN: AGEBAX
COUNTRY: Belgium
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 11 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Intralesional recombinant interferon alpha-2b in Peyronie's disease.
AB OBJECTIVE: To evaluate interferon alpha-2b (IFN) in the treatment of Peyronie's disease (PD) since IFN exerts **antifibrotic** action through collagen synthesis inhibition and **fibrolysis** stimulation. METHODS: The study comprised 34 patients, aged 31 to 63, with clinical and ultrasonographic (US) diagnosis of PD, who gave their consent to enter the study. They had the disease for 10.1 .+-. 5.6 (2-22) months. Ten million IU of IFN were injected intralesionally, twice weekly for 14 weeks or less if there was complete remission. Clinical evaluation included penis angle at erection, sexual dysfunction (pain, possibility of intercourse) and palpable plaque. Plaque size was evaluated by US. Systemic and local adverse reactions, and anti-IFN antibodies were monitored as well. RESULTS: Sexual dysfunction disappeared in 19/24 (79.2%) patients with this disorder, palpable lesions in 21/34 (62%), angle at erection in 15/32 (47%), and pain in 16/17 (94%). Complete clinical response was achieved in 16/34 patients (47%). Ultrasonographic response rate was 88%, (53% complete). Plaque size decreased from 56.7 .+-. 42.9 (median: 35.4) before treatment to 12.7 .+-. 22.6 mm2 (median: 0) ($p < 0.00001$; Wilcoxon's paired test). Clinical and US responses correlated. No patient showed progression. Eight of 9 patients in whom other treatments had failed responded to IFN therapy (5 complete). The main systemic adverse reaction in most patients (mild or moderate) was the flu-like syndrome expected for IFN. Local reactions, more related to the administration procedure than to IFN itself, were small hematoma (10 patients), edema (3), cysts that were excised surgically (2), and venous leak (1). No patient developed anti-IFN antibodies. CONCLUSIONS: IFN treatment can be a suitable option for the management of PD. The results appear to be better than those achieved with other procedures. Further works should include comparative studies, long-term follow-up of treated patients, and alternative ways of administration.
ACCESSION NUMBER: 2000338375 EMBASE
TITLE: Intralesional recombinant interferon alpha-2b in Peyronie's disease.
AUTHOR: Astorga R.; Cantero O.; Contreras D.; Del Rio-Martin A.; Labarta-Beceiro V.; Gutierrez-Elvirez A.; Lima-Lopez M.A.; Lopez-Saura P.
CORPORATE SOURCE: Dr. A. Del Rio-Martin, Center for Biological Research, Apartado Postal 6996, Havana, Cuba.
clintr@cigbdec.cigb.edu.cu
SOURCE: Archivos Espanoles de Urologia, (2000) 53/7 (665-671).
Refs: 22
ISSN: 0004-0614 CODEN: AEURAB
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English; Spanish

L11 ANSWER 12 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Interferon-.alpha.(2b) increases **fibrolysis** in fibrotic livers from bile duct ligated rats: Possible participation of the plasminogen activator.

AB Interferons are known to prevent liver collagen by an antifibrogenic mechanism that involves mRNA procollagen regulation. The aim of the present work was to determine whether interferon could also decrease collagen by increasing its degradation. Fibrosis was induced in male Wistar rats by double ligation and section of the common bile duct. Interferon-.alpha.(2b) (100,000 IU/rat s.c.) was administered to bile duct ligated rats daily after surgery for 4 weeks. Interferon increased the capacity of the liver to degrade type I and III collagens and matrigel. In addition, the plasminogen activator activity also increased. Since plasminogens are thought to be key participants in the balance of proteolytic activities that regulate extracellular matrix degradation, their elevation may also provide another **antifibrotic** (proteolytic) mechanism of action of interferon.

ACCESSION NUMBER: 95370247 EMBASE
DOCUMENT NUMBER: 1995370247
TITLE: Interferon-.alpha.(2b) increases **fibrolysis** in fibrotic livers from bile duct ligated rats: Possible participation of the plasminogen activator.
AUTHOR: Rodriguez-Fragoso L.; Gonzalez M.P.; Muriel P.
CORPORATE SOURCE: Dept. Pharmacology and Toxicology, CINVESTAV-IPN, Apdo. Postal 14-740,Mexico DF 07000, Mexico
SOURCE: Pharmacology, (1995) 51/6 (341-346).
ISSN: 0031-7012 CODEN: PHMGBN
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 13 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

TI Connective tissue polypeptides in serum as parameters to monitor **antifibrotic** treatment in hepatic fibrogenesis.

AB With the potential to specifically inhibit hepatic collagen synthesis a demand for serum tests to monitor the effectiveness of such treatment is expected. Serum assays for connective tissue polypeptides offer the potential to assess the dynamics of accumulation, i.e., fibrogenesis, and removal, i.e., **fibrolysis**, of the hepatic connective tissue on a regular and frequent basis. Several assays for circulating connective tissue polypeptides may be of use in fibrogenic liver diseases. Whereas an increase of the aminoterminal propeptide of type III procollagen (PIIINP) appears to be related to fibrogenesis, the propeptides of type IV procollagen (PIVNP, PIVCP) and laminin mirror enhanced basement membrane turnover in active fibrosis. Collagen type VI (CVI) and undulin (Un) rather reflect **fibrolysis** and remodelling of the interstitial connective tissue. Although the circulating antigens measured by these assays are heterogeneous, which often complicates the interpretation of elevated serum levels, it is likely that firm conclusions can be drawn as to the ongoing fibrogenesis, **fibrolysis** or both, once individual patients are followed with a combined measurement of two or three of these connective tissue parameters. Since 'easy to perform' assays are currently developed, such as therapy control seems practicable.

ACCESSION NUMBER: 91349022 EMBASE
DOCUMENT NUMBER: 1991349022
TITLE: Connective tissue polypeptides in serum as parameters to monitor **antifibrotic** treatment in hepatic fibrogenesis.
AUTHOR: Schuppan D.

CORPORATE SOURCE: Abt. fur Gastroenterologie, Klinikum Steglitz, Freie Universitat, Hindenburgdamm 30,1000 Berlin 45, Germany
SOURCE: Journal of Hepatology, (1991) 13/SUPPL. 3 (S17-S25). ISSN: 0168-8278 CODEN: JOHEEC
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
048 Gastroenterology
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

L11 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2003 ACS
TI Hepatitis C and liver fibrosis
AB A review. Chronic hepatitis C progresses to cirrhosis within 20 yr in an estd. 20-30% of patients, while running a relatively uneventful course in most others. Certain HCV proteins, such as core and NS5A, can induce derangement of lipid metab. or alter signal transduction of infected hepatocytes which leads to the prodn. of reactive oxygen radicals and profibrogenic mediators, in particular TGF-.beta.1. TGF-.beta.1 is the strongest known inducer of fibrogenesis in the effector cells of hepatic fibrosis, i.e. activated hepatic stellate cells and myofibroblasts. However, fibrogenesis proceeds only when addnl. profibrogenic stimuli are present, e.g. alc. exposure, metabolic disorders such as non-alc. steatohepatitis, or coinfections with HIV or Schistosoma mansoni that skew the immune response towards a Th2 T cell reaction. Furthermore, profibrogenic polymorphisms in genes that are relevant during fibrogenesis have been disclosed. This knowledge will make it possible to identify those patients who are most likely to progress and who need antiviral or **antifibrotic** therapies most urgently. However, even the best available treatment, the combination of pegylated interferon and ribavirin, which is costly and fraught with side effects, eradicates HCV in only 50% of patients. While the suggestive **antifibrotic** effect of interferons (IF-.gamma. > .alpha.,.beta.), irresp. of viral elimination, has to be proven in randomized prospective studies, addnl., well tolerated and cost-effective **antifibrotic** therapies have to be developed. The combination of cytokine strategies, e.g. inhibition of the key profibrogenic mediator TGF-.beta., with other potential **antifibrotic** agents appears promising. Such adjunctive agents could be silymarin, sho-saiko-to, halofuginone, phosphodiesterase inhibitors, and endothelin-A-receptor or angiotensin antagonists. Furthermore, drug targeting to the fibrogenic effector cells appears feasible. Together with the evolving validation of serol. markers of hepatic fibrogenesis and **fibrolysis** an effective and individualized treatment of liver fibrosis is anticipated.

ACCESSION NUMBER: 2003:515824 HCAPLUS
TITLE: Hepatitis C and liver fibrosis
AUTHOR(S): Schuppan, D.; Krebs, A.; Bauer, M.; Hahn, E. G.
CORPORATE SOURCE: Department of Medicine I, University of Erlangen-Nuernberg, Germany
SOURCE: Cell Death and Differentiation (2003), 10(1, Suppl. 1), S59-S67
CODEN: CDDIEK; ISSN: 1350-9047
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2003 ACS
TI Hepatitis C and liver fibrosis
AB Chronic hepatitis C progresses to cirrhosis within 20 yr in an estd. 20-30% of patients, while running a relatively uneventful course in most others. Certain HCV proteins, such as core and NS5A, can induce

derangement of lipid metab. or alter signal transduction of infected hepatocytes which leads to the prodn. of reactive oxygen radicals and profibrogenic mediators, in particular TGF-.beta.1. TGF-.beta.1 is the strongest known inducer of fibrogenesis in the effector cells of hepatic fibrosis, i.e. activated hepatic stellate cells and myofibroblasts. However, fibrogenesis proceeds only when addnl. profibrogenic stimuli are present, e.g. alc. exposure, metabolic disorders such as non-alc. steatohepatitis, or coinfections with HIV or Schistosoma mansoni that skew the immune response towards a Th2 T cell reaction. Furthermore, profibrogenic polymorphisms in genes that are relevant during fibrogenesis have been disclosed. This knowledge will make it possible to identify those patients who are most likely to progress and who need antiviral or **antifibrotic** therapies most urgently. However, even the best available treatment, the combination of pegylated interferon and ribavirin, which is costly and fraught with side effects, eradicates HCV in only 50% of patients. While the suggestive **antifibrotic** effect of interferons (IF-.gamma.>.alpha.,.beta.), irresp. of viral elimination, has to be proven in randomised prospective studies, addnl., well tolerated and cost-effective **antifibrotic** therapies have to be developed. The combination of cytokine strategies, e.g. inhibition of the key profibrogenic mediator TGF-.beta., with other potential **antifibrotic** agents appears promising. Such adjunctive agents could be silymarin, sho-saiko-to, halofuginone, phosphodiesterase inhibitors, and endothelin-A-receptor or angiotensin antagonists. Furthermore, drug targeting to the fibrogenic effector cells appears feasible. Together with the evolving validation of serol. markers of hepatic fibrogenesis and **fibrolysis** an effective and individualised treatment of liver fibrosis is anticipated.Cell Death and Differentiation (2003) 10, S59-S67.

ACCESSION NUMBER: 2003:229754 HCAPLUS
TITLE: Hepatitis C and liver fibrosis
AUTHOR(S): Schuppan, D.; Krebs, A.; Bauer, M.; Hahn, E. G.
CORPORATE SOURCE: Department of Medicine I, University of Erlangen-Nuernberg, Germany
SOURCE: Cell Death and Differentiation (2003), 10(Suppl. 1), S59-S67
CODEN: CDDIEK; ISSN: 1350-9047
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

L11 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2003 ACS
TI Serum markers and therapeutic approaches to fibrosis
AB A review with refs. on various serum markers and potential **antifibrotic** agents for liver fibrosis. Fibrosis results from excessive accumulation of extracellular matrix. Most of the serum fibrosis markers appear to reflect fibrinogenesis rather than **fibrolysis**. Serum markers open the possibility to assess the future evolution of fibrosis and the effect of potential **antifibrotic** treatment in an individual patient and on a frequent basis.

ACCESSION NUMBER: 2002:178710 HCAPLUS
DOCUMENT NUMBER: 137:210171
TITLE: Serum markers and therapeutic approaches to fibrosis
AUTHOR(S): Schuppan, D.; Bauer, M.; Herold, C.; Hahn, E. G.
CORPORATE SOURCE: Medizinische Klinik I mit Poliklinik, Universitat Erlangen-Nurnberg, Erlangen, 91054, Germany
SOURCE: Falk Symposium (2000), 116A(Chronic Hepatitis), 189-195
CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2003 ACS
TI The **antifibrotic** effects of D-penicillamine in liver fibrosis animal
AB One of therapeutics in liver disease (Morus Wilson) is D-penicillamine (D-pen: D-3-mercapto-valin). Esp. the crosslinking of collagen mols. could be inhibited by D-pen in extracellular space. In this study we investigated the **antifibrotic** effects of D-pen in rats with liver fibrosis induced by bile duct ligation and scission (NDL/S). Rats were treated for 4 wk with D-pen after BDL/S operation or sham operation. The balance between fibrogenesis-marker (PNIIIP) and the **fibrolysis**-maker (PNIVP) were obsd. in sera by RIA, and the parameter of collagen deposition in liver tissue (hydroxyproline: HYP) was measured by colorimetry. The wt. of liver in BDL/S operated group was increased significantly in compared with sham operation group (15.2 g.+-.1.1, vs. 11.9 g.+-.3.9:). The rats group treated by D-pen showed the lower level of PNIIIP (6.7 ng/mL.+-.1.5 vs. 9.5 ng/mL.+-.2.8) and the higher value of PIVCP (14.0 ng/mL.+-.1.9 vs. 7.9 ng/mL.+-.1.5) in sera that compared to untreated rats. The content of HYP was decreased by 141% in BDL/S with D-pen treated group than that of it in BDL/S group. No correlation was revealed between collagen parameters in sera and HYP in lever tissue of BDL/S operated and D-pen treated rats. The group treated with D-pen showed the lower value of clin. biochem. parameters (GOT: glutamate oxalacetate transaminase, Total-Bilirubin) in compared with only BDL/S operated rats, but the value of GPT (glutamate pyruvate transaminase) and Alk. phosphatase in two BDL/S groups was nearly same. In the histol. finding, we obsd. mild bile duct proliferation, weak inflammation and fibrosis in BDL/S with D-pen treated group, but BDL/S operated group showed the formation of septum (island of hepatocytes), massive bile duct proliferation. This result represents that the BDL/S operation induces liver fibrosis (cirrhosis) in 4 wk, and D-pen inhibits the synthesis of collagen weakly and stimulates the degrdn. of collagen in the extracellular space. We conclude that the monitoring of PNIIIP, PIVCP in sera is useful parameter for screening of **antifibrotic** effect, and D-pen delay the liver fibrosis.

ACCESSION NUMBER: 1996:717771 HCAPLUS
DOCUMENT NUMBER: 126:1141
TITLE: The **antifibrotic** effects of D-penicillamine in liver fibrosis animal
AUTHOR(S): Kim, Ki Young; Yun, Ki Jung; Moon, Huyng Bae
CORPORATE SOURCE: Pathology, College Medicine, Wonkwang University, Ikdan, A507-749, S. Korea
SOURCE: Yakhak Hoechi (1996), 40(5), 550-557
CODEN: YAHOA3; ISSN: 0513-4234
PUBLISHER: Pharmaceutical Society of Korea
DOCUMENT TYPE: Journal
LANGUAGE: Korean

L11 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2003 ACS
TI Interferon-.alpha.2b increases **fibrolysis** in fibrotic livers from bile duct ligated rats: possible participation of the plasminogen activator
AB Interferons are known to prevent liver collagen by an antifibrogenic mechanism that involves mRNA procollagen regulation. The aim here was to det. whether interferon could also decrease collagen by increasing its degrdn. Fibrosis was induced in male Wistar rats by double ligation and section of the common bile duct. Interferon-.alpha.2b (100,000 IU/rat s.c.) was administered to bile duct ligated rats daily after surgery for 4 wk. Interferon increased the capacity of the liver to degrade type I and III collagens and Matrigel. In addn., the plasminogen activator activity also increased. Since plasminogens are thought to be key participants in the balance of proteolytic activities that regulate extracellular matrix degrdn. their elevation may also provide another **antifibrotic**

(proteolytic) mechanism of action of interferon.
ACCESSION NUMBER: 1996:22283 HCAPLUS
DOCUMENT NUMBER: 124:84541
TITLE: Interferon-.alpha.2b increases **fibrolysis** in fibrotic livers from bile duct ligated rats: possible participation of the plasminogen activator
AUTHOR(S): Rodriguez-Fragoso, Lourdes; Gonzalez, M. Patricia; Muriel, Pablo
CORPORATE SOURCE: Dep. Gastroenterol., Inst. Nac. Nutr. Salvador Zubiran, Mexico City, Mex.
SOURCE: Pharmacology (1995), 51(6), 341-6
CODEN: PHMGBN; ISSN: 0031-7012
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English

L11 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2003 ACS
TI Changes in connective tissue metabolism during alcohol-dependent liver fibrosis
AB A review, with 44 refs., describing the structures and properties of liver collagens and extracellular glycoproteins, mechanisms of alc.-induced fibrosis, and serum tests for the measurement of liver fibrogenesis/ **fibrolysis** and the effects of potential **antifibrotic** drugs.
ACCESSION NUMBER: 1989:2277 HCAPLUS
DOCUMENT NUMBER: 110:2277
TITLE: Changes in connective tissue metabolism during alcohol-dependent liver fibrosis
AUTHOR(S): Shuppan, D.; Hahn, E. G.; Riecken, E. O.
CORPORATE SOURCE: Med. Klin., Klin. Steglitz, Berlin, D-1000/45, Fed. Rep. Ger.
SOURCE: Zeitschrift fuer Gastroenterologie (1988), 26(Suppl. 3), 28-38
CODEN: ZGASAX; ISSN: 0044-2771
DOCUMENT TYPE: Journal; General Review
LANGUAGE: German

L11 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Hepatitis C and liver fibrosis.
AB Chronic hepatitis C progresses to cirrhosis within 20 years in an estimated 20-30% of patients, while running a relatively uneventful course in most others. Certain HCV proteins, such as core and NS5A, can induce derangement of lipid metabolism or alter signal transduction of infected hepatocytes which leads to the production of reactive oxygen radicals and profibrogenic mediators, in particular TGF-beta1. TGF-beta1 is the strongest known inducer of fibrogenesis in the effector cells of hepatic fibrosis, i.e. activated hepatic stellate cells and myofibroblasts. However, fibrogenesis proceeds only when additional profibrogenic stimuli are present, e.g. alcohol exposure, metabolic disorders such as non-alcoholic steatohepatitis, or coinfections with HIV or Schistosoma mansoni that skew the immune response towards a Th2 T cell reaction. Furthermore, profibrogenic polymorphisms in genes that are relevant during fibrogenesis have been disclosed. This knowledge will make it possible to identify those patients who are most likely to progress and who need antiviral or **antifibrotic** therapies most urgently. However, even the best available treatment, the combination of pegylated interferon and ribavirin, which is costly and fraught with side effects, eradicates HCV in only 50% of patients. While the suggestive **antifibrotic** effect of interferons (IF-gamma > alpha,beta), irrespective of viral elimination, has to be proven in randomised prospective studies, additional, well tolerated and cost-effective **antifibrotic** therapies have to be developed. The combination of cytokine strategies, e.g. inhibition of the key profibrogenic mediator TGF-beta, with other potential **antifibrotic** agents appears promising. Such adjunctive

agents could be silymarin, sho-saiko-to, halofuginone, phosphodiesterase inhibitors, and endothelin-A-receptor or angiotensin antagonists. Furthermore, drug targeting to the fibrogenic effector cells appears feasible. Together with the evolving validation of serological markers of hepatic fibrogenesis and **fibrolysis** an effective and individualised treatment of liver fibrosis is anticipated.

ACCESSION NUMBER: 2003:262296 BIOSIS
DOCUMENT NUMBER: PREV200300262296
TITLE: Hepatitis C and liver fibrosis.
AUTHOR(S): Schuppan, D. (1); Krebs, A.; Bauer, M.; Hahn, E. G.
CORPORATE SOURCE: (1) Department of Medicine I, Dep. of Gastroenterology and Hepatology, University of Erlangen-Nuernberg, Ulmenweg 18, 91054, Erlangen, Germany: detlef.schuppan@med1.imed.uni-erlangen.de Germany
SOURCE: Cell Death and Differentiation, (January 2003, 2003) Vol. 10, No. Supplement 1, pp. S59-S67. print.
ISSN: 1350-9047.
DOCUMENT TYPE: General Review
LANGUAGE: English

L11 ANSWER 21 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI The **antifibrotic** effects of D-penicillamine in liver fibrosis animal.
AB One of therapeutics in liver disease (morbus wilson) is D-penicillin (D-pen: D-3-mercapto-valin). Especially the cross of collagen molecules could be inhibited by D-pen in extracellular space. In this study we investigated the **antifibrotic** effects of D-pen in rats that were induced the liver fibrosis by bile duct ligation and scission (BDL/S). Rats were treated for 4 weeks with Dpen after BDL/S operation or sham operation. The balance between fibrogenesis-marker (PNIIIP) and the **fibrolysis**-maker (PNIVP) were observed in sera by RIA (radioimmunoassay). and the parameter of collagen deposition in liver tissue (hydroxyproline: HYP) was measured by colorimetry. The weight of liver in BDL/S operated group was increased significantly in compared with sham operation group (15.2 g +-1.1, vs 11.9 g+-3.9: p lt 0.005, p lt 0.05). The rats group treated by D-pen showed the lower level of PNIIIP (6.7 ng/ml+-0.5. vs 9.5 ng/ml+-2.8) and the higher value of PIVCP (14.0 ng/ml+-1.9, vs 7.9 ng/ml+-1.5) in sera that compared to untreated rats. The content of HYP was decreased by 141% in BDL/S with D-pen treated group than that of it in BDL/S group. No correlation was revealed between collagen parameters in sera and HYP in liver tissue of BDL/S operated and D-pen treated rats. The group treated with D-pen showed the lower value of clinical biochemistry parameters (GOT: glutamate oxalacetate transaminase, Total-Bilirubin) in compared with only BDL/S operated rats, but the value of GPT (glutamate pyruvate transaminase) and and Alkaline phosphatase in two BDL/S groups was nearly same. In the histological finding, we observed mild bile duct proliferation, weak inflammation and fibrosis in BDL/S with D-pen treated group, but BDL/S operated group showed the formation of septum (island of hepatocytes), massive bile duct proliferation. This result represents that the BDUS operation induces liver fibrosis (cirrhosis) in 4 weeks, and D-pen inhibits the synthesis of collagen weakly and stimulates the degradation of collagen in the extracellular space. We conclude that the monitoring of PNIIIP, PIVCP in sera is useful parameter for screening of **antifibrotic** effect, and D-pen delay the liver fibrosis.

ACCESSION NUMBER: 1997:24712 BIOSIS
DOCUMENT NUMBER: PREV199799323915
TITLE: The **antifibrotic** effects of D-penicillamine in liver fibrosis animal.
AUTHOR(S): Kim, Ki Young (1); Yun, Ki Jung; Moon, Huyng Bae
CORPORATE SOURCE: (1) Pathol., Coll. Med., Wonkwang Univ., Iksan 570-749 South Korea
SOURCE: Yakhak Hoeji, (1996) Vol. 40, No. 5, pp. 550-557.
ISSN: 0513-4234.

DOCUMENT TYPE: Article
LANGUAGE: Korean
SUMMARY LANGUAGE: English

L11 ANSWER 22 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Interferon-alpha-2b increases **fibrolysis** in fibrotic livers from bile duct ligated rats: Possible participation of the plasminogen activator.
AB Interferons are known to prevent liver collagen by an antifibrogenic mechanism that involves mRNA procollagen regulation. The aim of the present work was to determine whether interferon could also decrease collagen by increasing its degradation. Fibrosis was induced in male Wistar rats by double ligation and section of the common bile duct. Interferon-alpha-2b (100,000 IU/rat s.c.) was administered to bile duct ligated rats daily after surgery for 4 weeks. Interferon increased the capacity of the liver to degrade type I and III collagens and matrigel. In addition, the plasminogen activator activity also increased. Since plasminogens are thought to be key participants in the balance of proteolytic activities that regulate extracellular matrix degradation, their elevation may also provide another **antifibrotic** (proteolytic) mechanism of action of interferon.
ACCESSION NUMBER: 1996:112785 BIOSIS
DOCUMENT NUMBER: PREV199698684920
TITLE: Interferon-alpha-2b increases **fibrolysis** in fibrotic livers from bile duct ligated rats: Possible participation of the plasminogen activator.
AUTHOR(S): Rodriguez-Fragoso, Lourdes; Gonzalez, M. Patricia; Muriel, Pablo (1)
CORPORATE SOURCE: (1) Dep. Pharmacology Toxicology, CINVESTAV-IPN, Apdo. Postal 14-740, Mexico DF 07000 Mexico
SOURCE: Pharmacology (Basel), (1995) Vol. 51, No. 6, pp. 341-346. ISSN: 0031-7012.
DOCUMENT TYPE: Article
LANGUAGE: English

L11 ANSWER 23 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Extracellular martix serum markers (ECMSM) in alcoholic liver disease.
ACCESSION NUMBER: 1995:406044 BIOSIS
DOCUMENT NUMBER: PREV199598420344
TITLE: Extracellular martix serum markers (ECMSM) in alcoholic liver disease.
AUTHOR(S): Chossegros, Philippe
CORPORATE SOURCE: Serv. d'Hepatogastroenterol., Hotel Dieu, Lyon France
SOURCE: Journal of Hepatology, (1995) Vol. 22, No. SUPPL. 2, pp. 96-99.
ISSN: 0168-8278.
DOCUMENT TYPE: Article
LANGUAGE: English

L11 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **Antifibrotic** effect of ursodeoxycholic acid in PBC stage I and II is suggested by serum parameters of fibrogenesis and **fibrolysis**.
ACCESSION NUMBER: 1993:354916 BIOSIS
DOCUMENT NUMBER: PREV199345038341
TITLE: **Antifibrotic** effect of ursodeoxycholic acid in PBC stage I and II is suggested by serum parameters of fibrogenesis and **fibrolysis**.
AUTHOR(S): Schuppan, D. (1); Stoelzel, U.; Somasundaram, R.; Bergs, C.; Hartung, J.; Oesterling, C.; Riecken, E. O.
CORPORATE SOURCE: (1) Dep. Gastroenterol., Steglitz Med. Sch., Free Univ. Berlin, Berlin Germany
SOURCE: Gastroenterology, (1993) Vol. 104, No. 4 SUPPL., pp. A987. Meeting Info.: 94th Annual Meeting of the American

Gastroenterological Association Boston, Massachusetts, USA
May 15-21, 1993
ISSN: 0016-5085.
DOCUMENT TYPE: Conference
LANGUAGE: English

L11 ANSWER 25 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI CONNECTIVE TISSUE POLYPEPTIDES IN SERUM AS PARAMETERS TO MONITOR **ANTIFIBROTIC** TREATMENT IN HEPATIC FIBROGENESIS.
AB With the potential to specifically inhibit hepatic collagten synthesis a demand for serum tests to monitor the effectiveness of such treatment is expected. Serum assays for connective tissue polypeptides offer the potential to assess the dynamics of accumulation, i.e., fibrogenesis, and removal, i.e., **fibrolysis**, of the hepatic connective tissue on a regular and frequent basis. Several assays for circulating connective tissue polypeptides may be of use in fibrogenic liver diseases. Whereas an increase of the aminoterminal propeptide of type III procollagen (PIIINP) appears to be related to fibrogenesis, the propeptides of type IV procollagen (PIVNP, PIVCP) and laminin mirror enhanced basement membrane turnover in active fibrosis. Collagen type VI (CVI) and undulin (Un) rather reflect **fibrolysis** and remodeling of the interstitial connective tissue. Although the circulating antigens measured by these assays are heterogeneous, which often complicates the interpretation of elevated serum levels, it is likely that firm conclusions can be drawn as to the ongoing fibrogenesis, **fibrolysis** or both, once individual patients are followed with a combined measurement of two or three of these connective tissue parameters. Since 'easy to perform' assays are currently developed, such as therapy control seems practicable.
ACCESSION NUMBER: 1992:75937 BIOSIS
DOCUMENT NUMBER: BA93:44392
TITLE: CONNECTIVE TISSUE POLYPEPTIDES IN SERUM AS PARAMETERS TO MONITOR **ANTIFIBROTIC** TREATMENT IN HEPATIC FIBROGENESIS.
AUTHOR(S): SCHUPPAN D
CORPORATE SOURCE: ABTEILUNG FUER GASTROENTEROLOGIE, KLINIKUM STEGLITZ, FREIEN UNIVERSITAET, HINDENBURGDAMM 30, 1000 BERLIN 45, GERMANY.
SOURCE: J HEPATOL (AMST), (1991) 13 (SUPPL 3), S17-S25.
CODEN: JOHEEC. ISSN: 0168-8278.
FILE SEGMENT: BA; OLD
LANGUAGE: English

=> s n-formylmethionyl-leucyl
L12 1092 N-FORMYLMETHIONYL-LEUCYL

=> s l12 and tyrosine
L13 57 L12 AND TYROSINE

=> s l13 and Phe
L14 2 L13 AND PHE

=> d l14 ti abs ibib tot

L14 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
TI The chemotactic factor **N-formylmethionyl-leucyl**-phenylalanine activates microtubule-associated protein 2 (MAP) kinase and a MAP kinase kinase in polymorphonuclear leukocytes
AB Incubation of human polymorphonuclear leukocytes (PMN) with either the chemotactic factor N-formyl-Met-Leu-**Phe** (FMLP) or phorbol 12-myristate 13-acetate (PMA) activates a kinase with phosphorylating activity towards a known microtubule-assocd. protein-2 (MAP) kinase substrate, the epidermal growth factor receptor peptide (T669). Activation of this enzyme by FMLP was maximal at 1 min, decreasing by 10 min. Activation by PMA was slightly slower than that by FMLP, but more

prolonged (maximal at 5 min, with no decrease by 20 min). The enzyme induced by either stimulant bound strongly to phenyl-Sepharose, had a mol. mass of 40 kDa on gel filtration and phosphorylated 3 MAP kinase substrates, i.e. MAP, myelin basic protein and the T669 peptide. The enzyme was identified as the 42 kDa MAP kinase (also known as extracellular-signal regulated kinase 2, ERK2). Stimulation of PMN with FMLP or PMA also induced a kinase kinase which phosphorylated human recombinant MAP kinase on threonine and **tyrosine**, with concomitant activation. Apparently, MAP kinase and the kinase kinase are involved in the activation of PMN by chemotactic factors such as FMLP.

ACCESSION NUMBER: 1993:189935 HCAPLUS
DOCUMENT NUMBER: 118:189935
TITLE: The chemotactic factor **N-formylmethionyl-leucyl**-phenylalanine activates microtubule-associated protein 2 (MAP) kinase and a MAP kinase kinase in polymorphonuclear leukocytes
AUTHOR(S): Thompson, H. Lorraine; Shiroo, Masahiro; Saklatvala, Jeremy
CORPORATE SOURCE: Cytokine Biochem. Dep., Strangeways Res. Lab., Cambridge, CB1 4RN, UK
SOURCE: Biochemical Journal (1993), 290(2), 483-8
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

L14 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Chemotactic peptide-induced activation of Ras in human neutrophils is associated with inhibition of p120-GAP activity.
AB The monomeric G-protein Ras is now considered to function as an initial regulator of multiple signaling pathways in both normal and transformed cell types. Adhesion and chemoattractant receptors are known to trigger activation of Ras in human neutrophils, but the signaling mechanism that activates Ras has only been partially elucidated. The present results show that in neutrophils, a time- and dose-dependent f-Met-Leu-**Phe** (FMLP)-induced activation of Ras is mediated by G-i2-proteins, because such activation is inhibited by pertussis toxin and because direct stimulation of heterotrimeric G-proteins with AlF-4- is sufficient to activate Ras. Pretreatment of neutrophils with **tyrosine** kinase inhibitors, i.e. genistein or erbstatin that completely block FMLP-stimulated protein **tyrosine** phosphorylations, did not affect the FMLP-induced activation of Ras. Moreover, FMLP did not induce any detectable translocation of Grb2 and Sos to the plasma membrane of neutrophils. Other signaling molecules, such as protein kinase C, phosphatidylinositol 3-kinase and Ca-2+, do not appear to be involved in the FMLP-induced Ras activation. Instead, stimulation of neutrophils with FMLP or C5a, the latter of which also activates G-i2-proteins, resulted in transient inhibition of the activity of Ras GTPase-activating proteins (GAP) with kinetics that correlated well with the kinetics of Ras activation. Moreover, decreased Ras-GAP activity was found in p120-GAP but not in neurofibromin immunoprecipitates of FMLP-stimulated cells. These results suggest that **tyrosine** kinase-dependent Ras exchange factors do not contribute to the FMLP-induced activation of Ras but that such activation is mediated via inhibition of p120GAP in neutrophils.

ACCESSION NUMBER: 1997:454889 BIOSIS
DOCUMENT NUMBER: PREV199799754092
TITLE: Chemotactic peptide-induced activation of Ras in human neutrophils is associated with inhibition of p120-GAP activity.
AUTHOR(S): Zheng, Limin (1); Dimitrijevic, Johan Vv Eckerdalan; Andersson, Tommy
CORPORATE SOURCE: (1) Div. Experimental Pathol., Wallenberg Lab., Floor 4, Lund Univ., U-MAS, S-205 02 Malmo Sweden
SOURCE: Journal of Biological Chemistry, (1997) Vol. 272, No. 37,

pp. 23448-23454.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 16:30:38 ON 18 JUL 2003)

FILE 'MEDLINE, USPATFULL, DGENE, EMBASE, WPIDS, FSTA, HCAPLUS, BIOSIS, CEN' ENTERED AT 16:31:14 ON 18 JUL 2003

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L1       100020 S FIBROSIS AND THERAPY
L2         7830 S L1 AND PEPTIDE
L3         2329 S F-MET-LEU-PHE
L4           34 S L3 AND L1
L5       260709 S CIRRHOSIS
L6        70721 S PULMONARY FIBROSIS
L7         2310 S L6 AND L5
L8            2 S L4 AND L7
L9         2635 S ANTIFIBROTIC?
L10         193 S FIBROLYSIS
L11          25 S L9 AND L10
L12        1092 S N-FORMYLMETHIONYL-LEUCYL
L13          57 S L12 AND TYROSINE
L14           2 S L13 AND PHE
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=> s l13 and l1
L15 0 L13 AND L1

=> d l13 ti abs ibib 1-10

L13 ANSWER 1 OF 57 MEDLINE

TI Macrophage stimulating protein (MSP) evokes superoxide anion production by human macrophages of different origin.

AB 1. Macrophage Stimulating Protein (MSP), a serum factor related to Hepatocyte Growth Factor, was originally discovered to stimulate chemotaxis of murine resident peritoneal macrophages. MSP is the ligand for Ron, a member of the Met subfamily of **tyrosine** kinase receptors. The effects of MSP on human macrophages and the role played in human pathophysiology have long been elusive. 2. We show here that human recombinant MSP (hrMSP) evokes a dose-dependent superoxide anion production in human alveolar and peritoneal macrophages as well as in monocyte-derived macrophages, but not in circulating human monocytes. Consistently, the mature Ron protein is expressed by the MSP responsive cells but not by the unresponsive monocytes. The respiratory burst evoked by hrMSP is quantitatively higher than the one induced by **N-formylmethionyl-leucyl**-phenylalanine and similar to phorbol myristate acetate-evoked one. 3. To investigate the mechanisms involved in NADPH oxidase activation, leading to superoxide anion production, different signal transduction inhibitors were used. By using the non selective **tyrosine** kinase inhibitor genistein, the selective c-Src inhibitor PP1, the **tyrosine** phosphatase inhibitor sodium orthovanadate, the phosphatidylinositol 3-kinase inhibitor wortmannin, the p38 inhibitor SB203580, the MEK inhibitor PD098059, we demonstrate that hrMSP-evoked superoxide production is mediated by **tyrosine** kinase activity, requires the activation of Src but not of PI 3-kinase. We also show that MAP kinase and p38 signalling pathways are involved. 4. These results clearly indicate that hrMSP induces the respiratory burst in human macrophages but not in monocytes, suggesting for the MSP/Ron complex a role of activator as well as of possible marker for human mature macrophages.

ACCESSION NUMBER: 2001652184 MEDLINE
DOCUMENT NUMBER: 21560312 PubMed ID: 11704649

TITLE: Macrophage stimulating protein (MSP) evokes superoxide anion production by human macrophages of different origin.
AUTHOR: Brunelleschi S; Penengo L; Lavagno L; Santoro C; Colangelo D; Viano I; Gaudino G
CORPORATE SOURCE: Department of Medical Sciences, University of Piemonte Orientale A. Avogadro, Via Solaroli, 17 - 28100 NOVARA, Italy.. sbrunell@med.unipmn.it
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Nov) 134 (6) 1285-95.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011114
Last Updated on STN: 20020317
Entered Medline: 20020315

L13 ANSWER 2 OF 57 MEDLINE

TI Ectodomain shedding of TGF-alpha and other transmembrane proteins is induced by receptor **tyrosine** kinase activation and MAP kinase signaling cascades.

AB A variety of transmembrane proteins, such as transforming growth factor-alpha (TGF-alpha), tumor necrosis factor-alpha (TNF-alpha) and L-selectin, undergo shedding, i.e. cleavage of the ectodomain, resulting in release of a soluble protein. Although the physiological relevance of ectodomain shedding is well recognized, little is known about the signaling mechanisms activating this process. We show that growth factor activation of cell surface **tyrosine** kinase receptors induces ectodomain cleavage of transmembrane TGF-alpha through activation of the Erk MAP kinase signaling cascade without the need for new protein synthesis. In addition, expression of constitutively activated MEK1 or its downstream target Erk2 MAP kinase was sufficient to stimulate TGF-alpha shedding. The basal cleavage level in the absence of exogenous growth factor stimulation was due to p38 MAP kinase signaling. Accordingly, a constitutively activated MKK6, a p38 activator, activated TGF-alpha shedding in the absence of exogenous stimuli. In addition to TGF-alpha shedding, these mechanisms also mediate L-selectin and TNF-alpha cleavage. Thus, L-selectin shedding by neutrophils, induced by **N -formylmethionyl-leucyl**-phenylalanine, was strongly inhibited by inhibitors of Erk MAP kinase or p38 MAP kinase signaling. Our results indicate that activation of Erk and p38 signaling pathways may represent a general physiological mechanism to induce shedding of a variety of transmembrane proteins.

ACCESSION NUMBER: 2000069326 MEDLINE
DOCUMENT NUMBER: 20069326 PubMed ID: 10601018
TITLE: Ectodomain shedding of TGF-alpha and other transmembrane proteins is induced by receptor **tyrosine** kinase activation and MAP kinase signaling cascades.
AUTHOR: Fan H; Derynck R
CORPORATE SOURCE: Department of Growth Development, Program in Cell Biology, University of California at San Francisco, San Francisco, CA 94143, USA.
CONTRACT NUMBER: RO1 CA54826 (NCI)
SOURCE: EMBO JOURNAL, (1999 Dec 15) 18 (24) 6962-72.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204

Entered Medline: 20000127

L13 ANSWER 3 OF 57 MEDLINE
TI Macrophages are essential for lymphocyte infiltration in formyl peptide-induced cholangitis in rat liver.
AB BACKGROUND/AIMS: Cholangitis in rats induced by N-formyl L-methionine L-leucine L-**tyrosine** (fMLT) is characterized by infiltration of mononuclear cells around bile ducts in portal tracts. METHODS: We investigated the initial process in fMLT-induced cholangitis histochemically. RESULTS: Administration of fMLT into the colons of adult male Wistar rats with acetate-induced colitis resulted in an infiltration of mostly macrophages and granulocytes into the portal tracts on day 1. Abnormal peroxidation as demonstrated by the nitro blue tetrazolium (NBT) reaction occurred in bile duct cells as well, although no apparent necrosis of the bile duct cells was observed. On day 4, the majority of the inflammatory cells in the portal tracts were CD4+ or CD8+ T lymphocytes. The oxidative products of the NBT reaction also disappeared from the bile duct cells. Administration of carrageenan, a potent inhibitor of macrophage function, resulted in a significant decrease in lymphocyte infiltration into the portal tracts. On day 8, portal inflammation subsided. CONCLUSIONS: In formyl peptide-induced cholangitis, macrophages and granulocytes may injure bile ducts transiently. Further, macrophages are necessary for the subsequent migration of T lymphocytes around the bile ducts.
ACCESSION NUMBER: 1999320969 MEDLINE
DOCUMENT NUMBER: 99320969 PubMed ID: 10395046
TITLE: Macrophages are essential for lymphocyte infiltration in formyl peptide-induced cholangitis in rat liver.
AUTHOR: Yamada S; Ishii M; Kisara N; Nagatomi R; Toyota T
CORPORATE SOURCE: Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.
SOURCE: LIVER, (1999 Jun) 19 (3) 253-8.
Journal code: 8200939. ISSN: 0106-9543.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991005
Last Updated on STN: 19991005
Entered Medline: 19990923

L13 ANSWER 4 OF 57 MEDLINE
TI Comparison of the roles of mitogen-activated protein kinase kinase and phosphatidylinositol 3-kinase signal transduction in neutrophil effector function.
AB Although it is known that many stimuli can activate mitogen-activated protein kinases (MAPKs) and phosphatidylinositol 3-kinases (PI3K) in human neutrophils, little is known concerning either the mechanisms or function of this activation. We have utilized a selective inhibitor of MAPK kinase (MEK), PD098059, and two inhibitors of PI3K, wortmannin and LY294002, to investigate the roles of these kinases in the regulation of neutrophil effector functions. Granulocyte/macrophage colony-stimulating factor, platelet-activating factor (PAF) and **N-formylmethionyl -leucyl**-phenylalanine are capable of activating both p44ERK1 and p42ERK2 MAPKs and phosphotyrosine-associated PI3K in human neutrophils. The activation of extracellular signal-related protein kinases (ERKs) is correlated with the activation of p21ras by both **tyrosine** kinase and G-protein-coupled receptors as measured by a novel assay for GTP loading. Wortmannin and LY294002 inhibit, to various degrees, superoxide generation, neutrophil migration and PAF release. Incubation with PD098059, however, inhibits only the PAF release stimulated by serum-treated zymosan. This demonstrates that, while neither MEK nor ERK kinases are involved in the activation of respiratory burst or neutrophil

migration, inhibition of PAF release suggests a potential role in the activation of cytosolic phospholipase A2. PI3K isoforms, however, seem to have a much wider role in regulating neutrophil functioning.

ACCESSION NUMBER: 1998070216 MEDLINE
DOCUMENT NUMBER: 98070216 PubMed ID: 9405284
TITLE: Comparison of the roles of mitogen-activated protein kinase kinase and phosphatidylinositol 3-kinase signal transduction in neutrophil effector function.
AUTHOR: Coffer P J; Geijsen N; M'rabet L; Schweizer R C; Maikoe T; Raaijmakers J A; Lammers J W; Koenderman L
CORPORATE SOURCE: Department of Pulmonary Diseases, G03.550, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.
SOURCE: BIOCHEMICAL JOURNAL, (1998 Jan 1) 329 (Pt 1) 121-30. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 20021219
Entered Medline: 19980211

L13 ANSWER 5 OF 57 MEDLINE

TI Inhibition of **N-formylmethionyl-leucyl**-phenylalanine-stimulated **tyrosine** phosphorylation and phospholipase D activation by quercetin in rabbit neutrophils.

AB We investigated the effect of bioflavonoid quercetin on **tyrosine** phosphorylation and phospholipase D (PLD, EC 3.1.4.4) activation in rabbit peritoneal neutrophils stimulated by **N-formylmethionyl-leucyl**-phenylalanine (fMLP). The quercetin dose-dependently inhibited degranulation and superoxide production in fMLP-stimulated neutrophils. A strong inhibitory effect of quercetin on the **tyrosine** phosphorylation of several proteins (40, 42, 43, 45, 46 and 75 kDa) was observed when the neutrophils were pretreated with different concentrations of quercetin. Furthermore, quercetin inhibited mitogen activated protein kinase (MAP kinase) and PLD activation induced by fMLP in a dose-dependent manner. The reduction in PLD activity was 30% at 0.1 microM and 70% at 100 microM of quercetin. These results suggest that impairment of neutrophil functions by quercetin may be due, at least in part, to inhibition of **tyrosine** phosphorylation and PLD activation.

ACCESSION NUMBER: 97405834 MEDLINE
DOCUMENT NUMBER: 97405834 PubMed ID: 9260878
TITLE: Inhibition of **N-formylmethionyl-leucyl**-phenylalanine-stimulated **tyrosine** phosphorylation and phospholipase D activation by quercetin in rabbit neutrophils.
AUTHOR: Takemura O S; Banno Y; Nozawa Y
CORPORATE SOURCE: Department of Biochemistry, Gifu University School of Medicine, Tsukasamachi, Japan.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1997 May 15) 53 (10) 1503-10. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 20000303
Entered Medline: 19970910

L13 ANSWER 6 OF 57 MEDLINE

TI Involvement of intracellular cyclic GMP and cyclic GMP-dependent protein kinase in alpha-elastin-induced macrophage chemotaxis.

AB alpha-Elastin with an average molecular mass of 70 kDa, an oxalic acid fragmentation product of highly purified insoluble elastin, induced the migration of macrophages, with maximum activity at 10(-1) microg/ml. Relative to the positive control of 10(-8) M **N-formylmethionyl-leucyl**-phenylalanine (fMLP), the responsiveness of macrophages to alpha-elastin was nearly the same. Checkerboard analysis demonstrated that the cell movement is chemotaxis and not chemokinesis. A homologous deactivation test showed the possibility of the existence of alpha-elastin-recognizing sites on macrophages. In connection with macrophage chemotaxis in response to alpha-elastin, the intracellular signaling pathway was examined. The guanosine 3', 5'-cyclic monophosphate (cGMP) level was enhanced in macrophages stimulated by alpha-elastin, whereas the adenosine 3',5'-cyclic monophosphate (cAMP) level was not. Chemotaxis assaying of macrophages treated with 8-Br cGMP- and dibutyryl cAMP-loaded macrophages indicated that cGMP promotes cell movement and cAMP suppresses cell locomotion. The possible involvement of protein kinases in the alpha-elastin signaling pathway was explored by use of inhibitors specific for cGMP-dependent protein kinase (PKG), cAMP-dependent protein kinase (PKA), protein kinase C (PKC), and **tyrosine** kinase. The macrophage chemotactic response to alpha-elastin was inhibited by the PKG inhibitor, but not by the PKA, PKC, or **tyrosine** kinase inhibitor. These results suggested that the increase in the cGMP level and the activation of PKG in macrophages are involved in alpha-elastin induced macrophage chemotaxis.

ACCESSION NUMBER: 97335931 MEDLINE
DOCUMENT NUMBER: 97335931 PubMed ID: 9192726
TITLE: Involvement of intracellular cyclic GMP and cyclic GMP-dependent protein kinase in alpha-elastin-induced macrophage chemotaxis.
AUTHOR: Kamisato S; Uemura Y; Takami N; Okamoto K
CORPORATE SOURCE: Department of Biochemical Engineering and Science, Kyushu Institute of Technology, Izuka, Fukuoka.
SOURCE: JOURNAL OF BIOCHEMISTRY, (1997 May) 121 (5) 862-7. Journal code: 0376600. ISSN: 0021-924X.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 19970916
Entered Medline: 19970904

L13 ANSWER 7 OF 57 MEDLINE

TI Effects of respiratory burst inhibitors on nitric oxide production by human neutrophils.

AB Human neutrophils (PMN) activated by **N-formylmethionyl-leucyl**-phenylalanine (fMLP) simultaneously release nitric oxide (.NO), superoxide anion (O2.-) and its dismutation product, hydrogen peroxide (H2O2). To assess whether .NO production shares common steps with the activation of the NADPH oxidase, PMN were treated with inhibitors and antagonists of intracellular signaling pathways and subsequently stimulated either with fMLP or with a phorbol ester (PMA). The G-protein inhibitor, pertussis toxin (1-10 micrograms/ml) decreased H2O2 yield without significantly changing .NO production in fMLP-stimulated neutrophils; no effects were observed in PMA-activated cells. The inhibition of **tyrosine** kinases by genistein (1-25 micrograms/ml) completely abolished H2O2 release by fMLP-activated neutrophils; conversely, .NO production increased about 1.5- and 3-fold with fMLP and PMA, respectively. Accordingly, orthovanadate, an inhibitor of phosphotyrosine phosphatase, markedly decreased .NO production and

increased O2.- release. On the other hand, inhibition of protein kinase C with staurosporine and the use of burst antagonists like adenosine, cholera toxin or dibutyryl-cAMP diminished both H2O2 and .NO production. The results suggest that the activation of the **tyrosine** kinase pathway in stimulated human neutrophils controls positively O2.- and H2O2 generation and simultaneously maintains .NO production in low levels. In contrast, activation of protein kinase C is a positive modulator for O2.- and .NO production.

ACCESSION NUMBER: 97311038 MEDLINE
DOCUMENT NUMBER: 97311038 PubMed ID: 9167937
TITLE: Effects of respiratory burst inhibitors on nitric oxide production by human neutrophils.
AUTHOR: Carreras M C; Riobo N A; Pargament G A; Boveris A; Poderoso J J
CORPORATE SOURCE: University Hospital, School of Medicine, University of Buenos Aires, Argentina.
SOURCE: FREE RADICAL RESEARCH, (1997 Apr) 26 (4) 325-34. Journal code: 9423872. ISSN: 1071-5762.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 20021218
Entered Medline: 19970717

L13 ANSWER 8 OF 57 MEDLINE
TI Synergistic activation of PtdIns 3-kinase by **tyrosine** -phosphorylated peptide and beta gamma-subunits of GTP-binding proteins.
AB Stimulation of differentiated THP-1 cells by insulin led to rapid accumulation of PtdIns(3,4,5)P3, a product of PtdIns 3-kinase. Stimulation of the GTP-binding-protein-linked receptor by **N-formylmethionyl-leucyl**-phenylalanine (fMLP) also induced the accumulation of PtdIns(3,4,5)P3 in the cells. The effect of insulin was, while that of fMLP was not, accompanied by increased PtdIns 3-kinase activity in the anti-phosphotyrosine immuno-precipitate. The combination of insulin and fMLP induced more PtdIns(3,4,5)P3 production than the sum of the individual effects. The insulin-induced recruitment of PtdIns 3-kinase activity in the anti-phosphotyrosine immunoprecipitate was unaffected by the combined treatment with fMLP. To investigate the mechanism underlying the synergistic accumulation of PtdIns(3,4,5)P3, we separated the cytosolic proteins of THP-1 cells on a Mono Q column. PtdIns 3-kinase activities were eluted in two peaks, and one of the peaks markedly increased on the addition of beta gamma-subunits of GTP-binding proteins (G beta gamma). The other peak was affected only slightly by G beta gamma, but was synergistically increased by G beta gamma and a **tyrosine**-phosphorylated peptide which was synthesized accordingly to the amino acid sequence of insulin receptor substrate-1. The activity in the latter fraction was completely immunoprecipitated by an antibody against the regulatory subunit of PtdIns 3-kinase (p85). These results suggest that the conventional PtdIns 3-kinase (p85/p110), which has been implicated in insulin-induced cellular events, or a closely related isoenzyme is controlled by a combination of a **tyrosine** -phosphorylated protein and a GTP-binding protein in intact cells.

ACCESSION NUMBER: 96313799 MEDLINE
DOCUMENT NUMBER: 96313799 PubMed ID: 8713074
TITLE: Synergistic activation of PtdIns 3-kinase by **tyrosine**-phosphorylated peptide and beta gamma-subunits of GTP-binding proteins.
AUTHOR: Okada T; Hazeki O; Ui M; Katada T
CORPORATE SOURCE: Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, University of Tokyo, Japan.
SOURCE: BIOCHEMICAL JOURNAL, (1996 Jul 15) 317 (Pt 2) 475-80.

Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 20000303
Entered Medline: 19960912

L13 ANSWER 9 OF 57 MEDLINE

TI Granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes phosphorylation and an increase in the activity of cytosolic phospholipase A2 in human neutrophils.

AB Incubation of human neutrophils with 500 pM granulocyte-macrophage colony-stimulating factor (GM-CSF) results in a rapid and time-dependent increase in the phosphorylation of cytosolic phospholipase A2 (cPLA2), which was reflected in a slower electrophoretic mobility of the enzyme. The GM-CSF-induced phosphorylation of cPLA2 was accompanied by a parallel and time-dependent increase in the enzyme activity. Preincubation of neutrophils with the **tyrosine** kinase inhibitor genistein caused inhibition of the GM-CSF-stimulated phosphorylation and activity of cPLA2. Immunoprecipitation of the enzyme following incubation of neutrophils with [32P]Pi shows that cPLA2 is phosphorylated by GM-CSF. Potato acid phosphatase caused dephosphorylation of the enzyme, indicating that cPLA2 is indeed phosphorylated by GM-CSF. The subcellular distribution of cPLA2 in GM-CSF-stimulated neutrophils revealed that the enzyme resides almost completely in the cytosolic fraction. Addition of Ca2+ to the lysis buffer before homogenization results in the translocation of the phosphorylated and the dephosphorylated forms of the enzyme to the membranes. Translocation of cPLA2 was also achieved after incubation with 0.1 microM **N-formylmethionyl-leucyl**
-phenyl-alanine (fMLP) after GM-CSF stimulation and when neutrophils were challenged with the Ca2+ ionophore A23187. EDTA and EGTA were unable to solubilize the translocated enzyme from the neutrophil membranes, indicating that cPLA2 is attached to the membranes by strong bonds and not merely due to ionic forces exerted by Ca2+. The inability of GM-CSF to promote arachidonic acid mobilization is probably due to the fact that GM-CSF does not cause an increase in intracellular Ca2+, which is necessary for the translocation of the enzyme to the membranes where its substrate(s) reside.

ACCESSION NUMBER: 96152533 MEDLINE
DOCUMENT NUMBER: 96152533 PubMed ID: 8573084
TITLE: Granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes phosphorylation and an increase in the activity of cytosolic phospholipase A2 in human neutrophils.
AUTHOR: Nahas N; Waterman W H; Sha'afi R I
CORPORATE SOURCE: Department of Physiology, University of Connecticut Health Center, Farmington 06030-3505, USA.
CONTRACT NUMBER: AI-28810-03 (NIAID)
HL-53786-06 (NHLBI)
SOURCE: BIOCHEMICAL JOURNAL, (1996 Jan 15) 313 (Pt 2) 503-8.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199603
ENTRY DATE: Entered STN: 19960315
Last Updated on STN: 19980206
Entered Medline: 19960301

L13 ANSWER 10 OF 57 MEDLINE

TI Morphological polarization of human polymorphonuclear leucocytes in

response to three different chemoattractants: an effector response independent of calcium rise and **tyrosine** kinases.

AB Chemoattractants such as interleukin-8, C5a and **N-formylmethionyl-leucyl**-phenylalanine induce a cytosolic calcium rise involved in triggering the secretory functions of human polymorphonuclear leucocytes. We studied the possible role of calcium rise in membrane ruffling, actin polymerization, filamentous actin distribution, and morphological polarization, which are all events contributing to chemotaxis. Membrane ruffling was assessed by right-angle light-scatter changes, the cellular content of polymerized actin by fluorescence of bodipy phallacidin, the intracellular distribution of filamentous actin by fluorescence microscopy and image digitization, and morphological polarization by scanning electron microscopy. Pretreatment of polymorphonuclear leucocytes with 50 microM BAPTA/AM, an intracellular calcium chelator, lowered the basal level in cell calcium and inhibited the transient calcium rise stimulated by 2 nM interleukin-8, 2 nM C5a, and 10 nM **N-formylmethionyl-leucyl**-phenylalanine. However, BAPTA pretreatment of polymorphonuclear leucocytes did not modify membrane ruffling, actin polymerization, filamentous actin distribution, and morphological polarization stimulated by chemoattractants. Downstream effectors may be protein **tyrosine** kinases. However, the **tyrosine** kinase inhibitor tyrphostin did not affect the cytoskeletal characteristics elicited by chemoattractants. Taken together, our results suggest that the transductional pathway leading to cytoskeleton organization and morphological polarization of polymorphonuclear leucocytes is different from that leading to secretion.

ACCESSION NUMBER: 95340705 MEDLINE
DOCUMENT NUMBER: 95340705 PubMed ID: 7615691
TITLE: Morphological polarization of human polymorphonuclear leucocytes in response to three different chemoattractants: an effector response independent of calcium rise and **tyrosine** kinases.
AUTHOR: Lepidi H; Zaffran Y; Ansaldi J L; Mege J L; Capo C
CORPORATE SOURCE: Unite INSERM U387, Hopital de Sainte-Marguerite, Marseille, France.
SOURCE: JOURNAL OF CELL SCIENCE, (1995 Apr) 108 (Pt 4) 1771-8. Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19970203
Entered Medline: 19950822

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E6            1      CLAGETTEN U F/AU
E7            1      CLAGG E A/AU
E8            1      CLAGG H/AU
E9            2      CLAGG H B/AU
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E11           1      CLAGGET C E/AU
E12           1      CLAGGETT A L/AU

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E5            1      CLAGETTE A D/AU
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E12           1      CLAGGETT A L/AU

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